DEVELOPMENT OF NEW SYNTHETIC METHODOLOGY : SYNTHETIC AND MECHANISTIC STUDY

A Thesis Submitted
in Partial Fulfilment of the Requirements
for the Degree of
DOCTOR OF PHILOSOPHY

by

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to the

DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY, KANPUR

NOVEMBER, 1989

Dedicated

to

My Parents

DEPARTMENT OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY KANPUR, INDIA

CERTIFICATE OF COURSE WORK

This is to certify that Mr. S. Baskaran has satisfactorily completed all the courses required for the Ph.D. degree program. The courses include:

Chm 505 Principles of Organic Chemistry

Chm 524 Modern Physical Methods in Chemistry

Chm 525 Principles of Physical Chemistry

Chm 545 Principles of Inorganic Chemistry

Chm 616 Chemistry of Organometallic Compounds

Chm 620 Frontiers in Biology

Chm 800 General Seminar

Chm 801 Graduate Seminar

Chm 900 Post-Graduate Research

Mr. S. Baskaran was admitted to the candidacy of the Ph. D. degree in March 1987 after he successfully completed the written and oral qualifying examinations.

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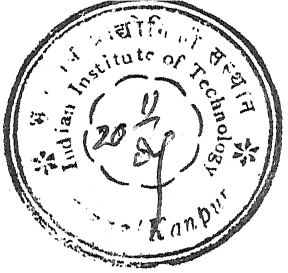

CERTIFICATE

Certified that the work contained in this thesis entitled "DEVELOPMENT OF NEW SYNTHETIC METHODOLOGY: SYNTHETIC AND MECHANISTIC STUDY" has been carried out by Mr. S. Baskaran under my supervision and the same has not been submitted elsewhere for a degree.

S. CHANDRASEKARAN
Thesis Supervisor

STATEMENT

I hereby declare that the matter embodied in this thesis. "Development of New Synthetic Methodology: Synthetic and Mechanistic Study", is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology, Kanpur, India, under the supervision of Prof. S. Chandrasekaran.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

(S. Baskaran)

Kanpur:
November 1989

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S. Baskaran

PREFACE

The thesis entitled "Development of New Synthetic Methodology: Synthetic and Mechanistic Study" is divided into three major chapters and Chapter I is subdivided into Part A and Part B. Chapter II is ramified into three parts A,B and C.

Chapter I: Oxidative transformations with Oxo-Chromium (VI) Reagents

Part A: Selective oxidative cleavage of enol ether double bonds. Application of this methodology for the synthesis of macrocyclic keto-lactones, substituted butanolides and the sex pheromone of the Japanese beetle Popillia japonica.

Part B: Studies on the mechanism of the substituent directed oxidative cyclization of tert - γ -hydroxy olefins to γ -lactones with oxo-chromium (VI) reagents.

Chapter II: Oxidative Transformations with Oxo-Manganese (VII) Reagent

Part A: Direct conversion of olefins to α-diketones/ α-hydroxy ketones with potassium permanganate supported on copper sulfate pentahydrate under heterogeneous conditions; Omega phase catalysis.

Part B: Oxidation of 1,5-hexadienes to 5-substituted butanolides with potassium permanganate supported on copper sulfate pentahydrate under heterogeneous conditions; Omega phase catalysis.

Part C: An improved procedure for the preparation of the versatile reagent, cetyltrimethylammonium permanganate (CTAP).

Chapter III : New synthetic methodology with Benzyltriethyl ammonium borohydride/chlorotrimethylsilane. Direct conversion of alkenes to alcohols and some interesting reactions with enol ethers.

In Chapter I, Part A, a facile and selective, oxidative cleavage of ketone derived enol ether double bonds with oxo-chromium (VI) reagents under anhydrous conditions has been studied. Bicyclic enol ethers, 9, 11, 13 and 15 afforded the

corresponding macrocyclic keto-lactones 10, 12, 14 and 16 respectively in high yields, under very mild reaction conditions. Oxo-chromium (VI) promoted, selective cleavage of electron rich carbon-carbon double bonds has been applied for the construction of butanolides having sensitive functional groups such as vinyl 4a, allyl 4b, benzyl 4c, ethynyl 4d etc., using a three step strategy :

i) Bromo etherification of γ-hydroxy olefins 1, using N-bromosuccinimide.

ii) Dehydro bromination to give enol ethers 3

iii) Selective cleavage of enol ether double bonds 3 to the corresponding butanolides 4 with oxo-chromium (VI) reagents.

The efficacy of this methodology has been exemplified in the synthesis of the Japanese beetle pheromone, Popillia japonica 31.

Chapter I, part B, deals with the studies on the mechanism of the substituent directed oxidative cyclization of tert-γ-hydroxy olefins to γ-lactones with oxo-chromium (VI) reagents. There are two closely related mechanistic pathways which can account for the formation of products:

i) Initial formation of a chromate ester A can guide the attack on the olefin (type A).

ii) The hydroxyl group can exert its effect on an activated complex B of the olefin (type B).

Partial support for the above mechanism comes from the following facts :

i) Trapping of the intermediates

ii) Converting the intermediates to the final product on treatment with oxo-chromium (VI) reagents.

iii) Isolation of the intermediates under controlled conditions.

The proposed mechanism was further supported by the reaction of compound 51 to keto-lactone 54 with oxo-chromium reagent, PCC.

Chapter II, Part A, describes the studies on the oxidation of olefins to α-diketones/α-hydroxy ketones with potassium permanganate supported on copper sulfate pentahydrate in presence of catalytic amount of water and tert. butyl alcohol. This procedure is complimentary to the existing Sharpless procedure. Unusual formation of the epoxides in this reaction increases with increase in lipophilicity of the substrates. Omega phase catalysis has been invoked to explain the case of formation of these products.

The oxidative transformation of 1,5-hexadienes with $KMnO_4/CuSO_4.5H_2O$ is the subject matter of Chapter II, Part B. Under conditions of omega phase catalysis, geranyl acetate 12 afforded the 5-membered lactone 14 and 6-membered lactone 15a. On the other hand its geometrical isomer, neryl acetate 13 yielded 5-membered lactone 14 and 6-membered lactone 15b, which is diastereo isomer of 15a (Scheme 9). Invoking Sharpless proposal, a plausible mechanism has also been delineated.

Chapter II, Part C, describes an improved procedure for the preparation of the versatile reagent, cetyltrimethylammonium

permanganate (CTAP), using two phase system, i.e., water and dichloromethane. The preparation has been scaled upto 100 g, using this procedure.

In Chapter III a new synthetic methodology for the direct conversion of alkenes to alcohols with benzyltriethylammonium borohydride in combination with chlorotrimethylsilane has been discussed. This methodology bypasses the formal oxidative work-up procedure which is involved in the hydroboration reaction. Alkenes having -OTHP or -OTHF ethers have also been converted to alcohols in good yields, whereas under normal hydroboration - oxidation conditions, the purification of products by distillation have led to explosions.

Mechanism of this unusual reaction has been investigated. Some data from the literature and NMR spectral analysis of an intermediate support the involvement of a silicon-boron complex in this reaction.

Reaction of cyclic enol ethers 30 and 32 with this reagent system, afforded the corresponding acyclic diols 31 and 33 respectively, whereas acyclic enol ether 36 yielded the alcohol 37.

CONTENTS

CHAPTER IA

OXIDATIVE TRANSFORMATIONS WITH OXO-CHROMIUM(VI) REAGENTS

IA.1 INTRODUCTION

Oxo-Chromium Reagents in Organic Synthesis

Oxo-chromium(VI) reagents are most versatile and extensively used oxidants for introducing oxygen into organic molecules.[1-7] Although chromium(VI) owing to its high oxidation potential, is capable of oxidizing almost all organic functional groups, it is often possible to perform selective oxidation to give largely just one single product by choosing proper reaction conditions and oxidant.[6,7] Several oxo-chromium(VI) reagents like chromic acid,[2] chromyl acetate,[8] chromyl chloride,[5,9] tert.butylchromate,[10] chromium trioxide pyridine complex (Sarett's reagent),[11] dipyridine chromium(VI) oxide (Collins' reagent),[12] pyridinium chlorochromate (PCC),[13] pyridinium dichromate (PDC),[14] 2,2'-bipyridinium chlorochromate [Bipy.$HCrO_3Cl$],[15] tetraalkylammonium chromate[16], solid supported chromium(VI) oxidants[17] and other chromium(VI) oxidants have been used for the different functional group transformations. Aqueous chromic acid[2] is a potent oxidant and other important variations of chromic acid oxidants include chromic acid in aqueous acetone (Jones' reagent),[18] the Kiliani's reagent[19] (H_2CrO_4, H_2SO_4, H_2O) in acetic acid, and chromium trioxide in anhydrous acetic acid

(Fieser's reagent).[20]

Albeit, chromium(V) is postulated[1-7] as a reactive intermediate formed during all the oxidations with chromium(VI), its utility is severely limited due to its hygroscopic and unstable nature. Earlier work from our laboratory has evinced the selectivity of this chromium(V) reagents for specific transformations like alcohols to carbonyl compounds,[21a] aldehydes to acids,[21b] cleavage of carbon-carbon double bonds,[21c] diols to lactones[21d] and hydroxy olefins to lactones.[21e]

Oxidation of Carbon-Carbon Double Bonds with Oxo-Chromium Reagents

The oxidation of double bonds with oxo-chromium(VI) reagents is usually of little synthetic interest, since the reaction leads in several cases to a variety of different products including carboxylic acids, carbonyl compounds, glycols, ketols and epoxides.[6,7] Double bond oxidation is further complicated by competitive oxidation at the allylic positions.[6] Aqueous medium generally favours oxidative cleavage of the double bond whereas anhydrous conditions lead to allylic attack or to the formation of partially oxidized products like epoxides and ketols.

Although the Jones' reagent is relatively unreactive towards olefinic linkage, in the presence of catalytic amount of mercuric acetate, terminal olefins can be oxidized to methyl ketones in good yields.[22] The oxidation of olefins with silver chromate-iodine provides a new and facile synthesis of α-iodo

ketones.[23] The chromic acid oxidation of carbon-carbon double bond does not appear to be synthetically useful, whereas chromic acid derivatives such as chromyl acetate and chromyl chloride are useful reagents for oxidizing olefins. The oxidation of highly substituted aromatic olefins with chromyl acetate gives the epoxides as the major product and small amount of benzpinacol carbonates.[24] The carbonate formation predominates when potassium acetate is used as a buffer.

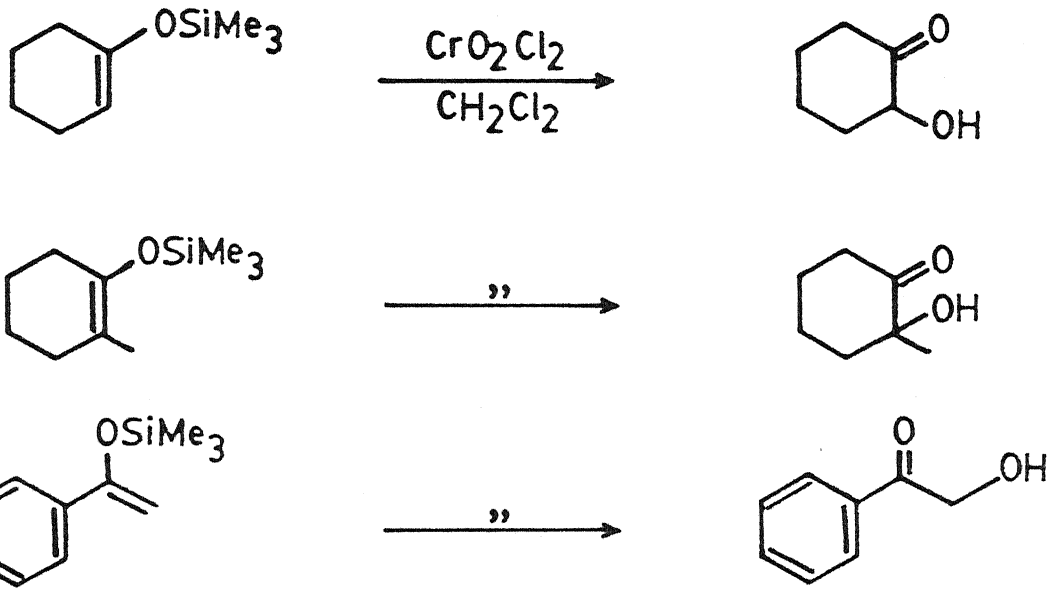
The products from the chromyl chloride oxidation of alkenes are strongly dependent on reaction conditions. The oxidation of olefins with chromyl chloride in dichloromethane[25] afforded aldehydes and ketones. On the other hand when the same reaction was carried out in acetone,[26] α-chloro ketone was obtained as the major product along with small amounts of cis-chlorohydrin and cis-dichloride.

The formation of cis-chlorohydrin and cis-dichloride with high stereoselectivity has been explained by invoking metallooxetane intermediate (**Scheme IB.1.6**).[26a]

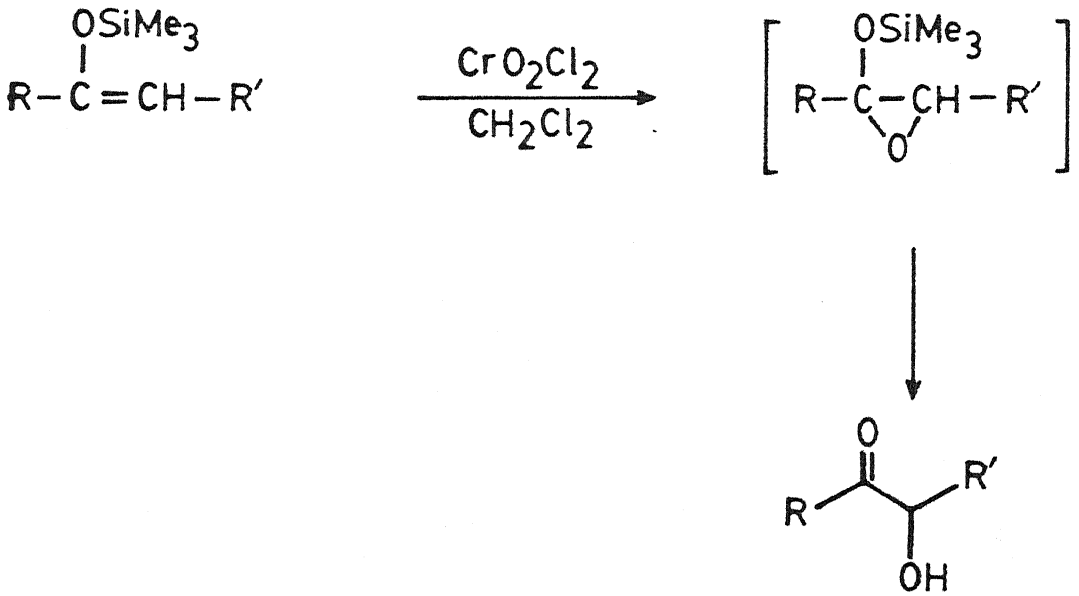
Chromyl chloride has been found to be a selective reagent for the conversion of silyl enol ethers to α-hydroxy ketones under very mild conditions[27] (**Scheme IA.1.1**).

Unlike other oxo-chromium(VI) oxidants, pyridinium chlorochromate (PCC) does not oxidize simple carbon-carbon double bonds or triple bonds.[28] However, PCC can oxidize activated carbon-carbon double bonds.[29] An unusual regio-specificity of PCC is shown in the oxidation of 5-bromo-2-furylcarbinols to γ-

Scheme-IA-1·1



Mechanism:

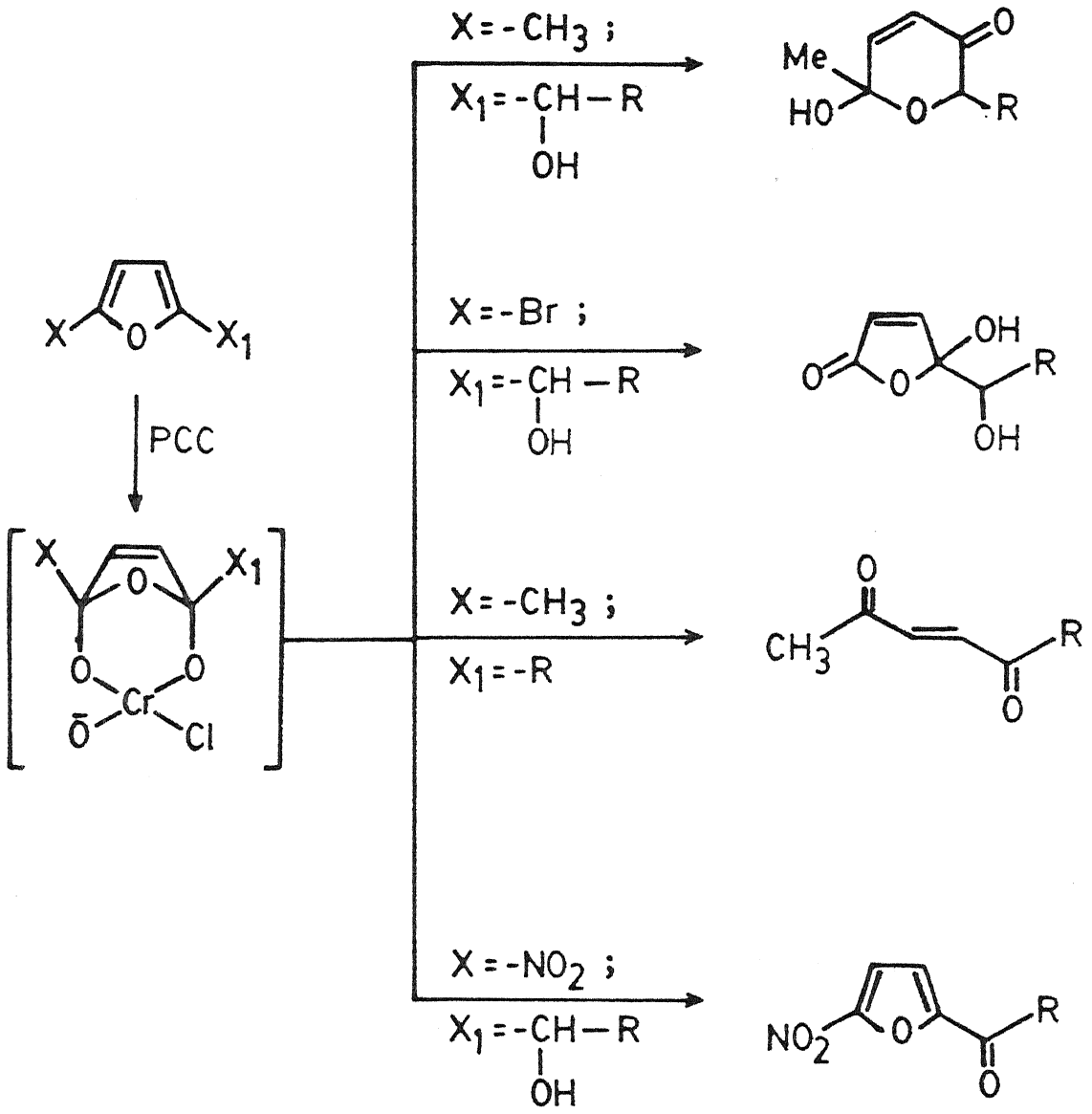


hydroxy butenolides[30] (**Scheme IA.1.2**). This reaction shows a high chemoselectivity leading only to attack of the aromatic ring, leaving the secondary alcoholic function untouched. When the heteroaromatic nucleus is deactivated by the presence of a nitro group in position 5, the oxidant preferentially oxidizes the alcoholic function, affording 5-nitro-2-furyl ketones[31] (**Scheme IA.1.2**). 5-Methyl-2-furylcarbinols undergo oxidation, on treatment with PCC, to give the biologically important ring enlarged products[32] (**Scheme IA.1.2**). On the other hand, 2,5-dialkylfurans undergo oxidative ring fission to $\alpha\beta$-unsaturated-γ-dicarbonyl compounds in good yields[33] (**Scheme IA.1.2**).

A general mechanism[32] for the oxidation of furan derivatives by PCC has been proposed which involves the initial formation of cyclic chromate ester intermediate by 1,4-electrophilic attack of chlorochromate anion upon the furan ring. Subsequent decomposition of the cyclic chromate ester intermediate by heterolytic cleavage of the Cr-O bond leads to α,β-unsaturated -γ dicarbonyl compounds, hydroxy pyranones, or hydroxy butenolides. Furthermore, the formation of 6-hydroxy-2H-pyran-3(6H)-ones from 5-alkyl-2-furylcarbinols involves a nucleophilic participation of the alcoholic function of the side chain in heterolysis (**Scheme IA.1.2**).

Piancatelli *et al.*[34] reported an unusual oxidation of enol ethers by pyridinium chlorochromate (PCC) to esters and lactones. The proposed mechanism involves an unstable cyclic chromate ester intermediate, which decomposes by chromium-oxygen bond cleavage and subsequent 1,2-hydride shift resulting in the

Scheme-IA-1·2


X=-CH3 ;
X1=-CH-R
OH
X=-Br ;
X1=-CH-R
OH
X=-CH3 ;
X1=-R
X=-NO2 ;
X1=-CH-R
OH
PCC
X
X1
O
Me
HO
R
OH
CH3
NO2
Cr
Cl

formation of ester or lactone (**Scheme IA.1.3**).

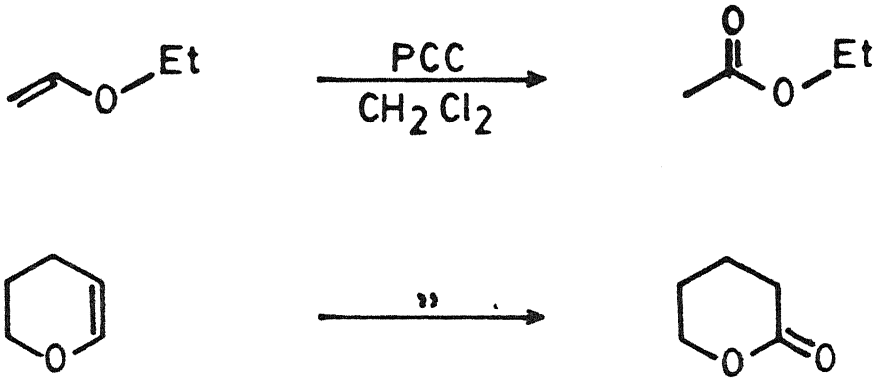
Pyridinium dichromate/tert.butyl hydroperoxide reagent system,[35] which has been developed in our laboratory, has been found to be an excellent oxidant for the conversion of cyclic enol ethers to the corresponding α,β-unsaturated lactones under very mild conditions[36] (**Scheme IA.1.4**).

In the synthesis of Δ^{16}-20-ketosteroids from sapogenins, chromic acid in acetic acid has been used to cleave the enol ether double bond to form keto-acetate[37] in low yield (**Scheme IA.1.5**). Since chromic acid is known to cleave carbon-carbon double bond to a variety of products, this reagent cannot be applied for the selective cleavage of enol ether double bond in presence of isolated double bond.

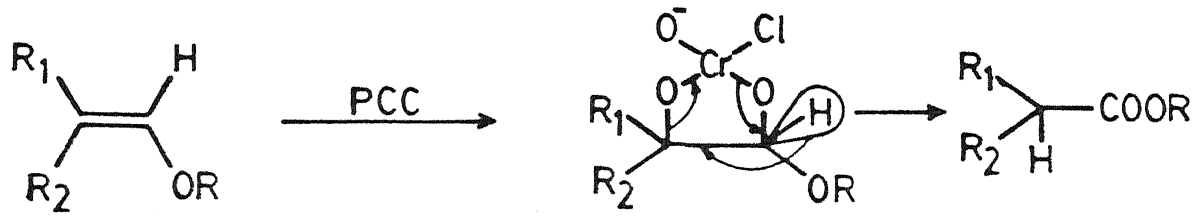
Synthesis of Macrolides by Oxidative Cleavage of Bicyclic Enol Ethers

Many macrolides have high physiological potency including antibiotic, antitumor, cytostatic and platelet aggregation activities. Great progress has been made in recent years towards stereo-controlled synthesis of polysubstituted macrolides.[38] The chemistry of medium- and large-ring lactones has also attracted considerable attention because many of the molecules belonging to these groups have revealed diverse and significant biological activities.[39] The methods used to synthesize these classes of lactone, published so far, have been broadly classified into three categories : (a) cyclization of ω-hydroxy acids, (b) cyclization of straight chain esters by carbon-carbon

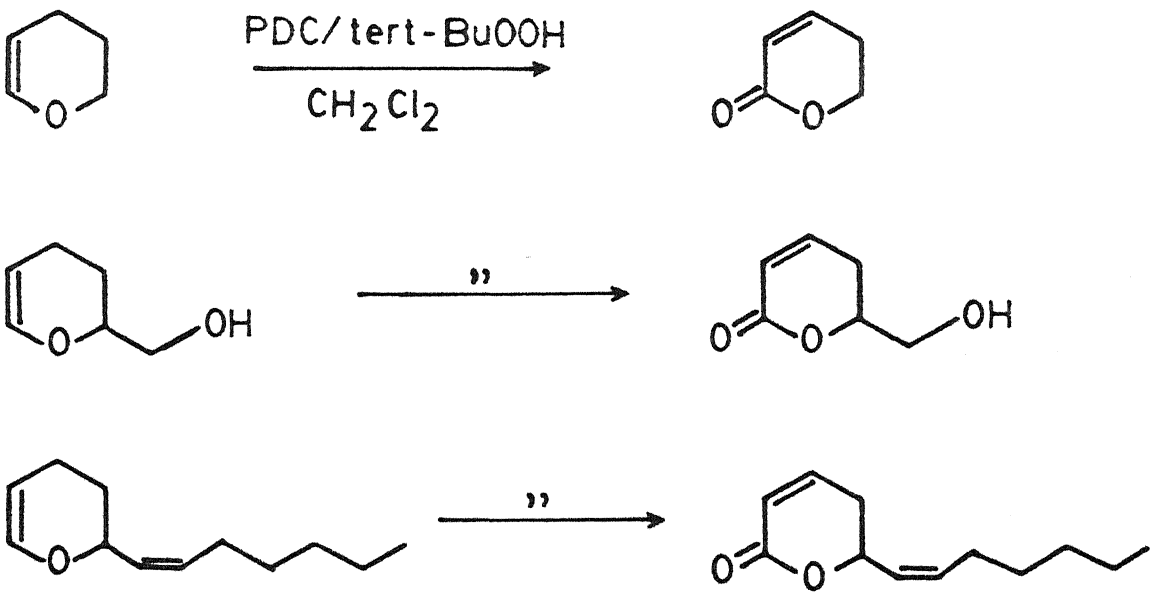
Scheme-IA-1·3



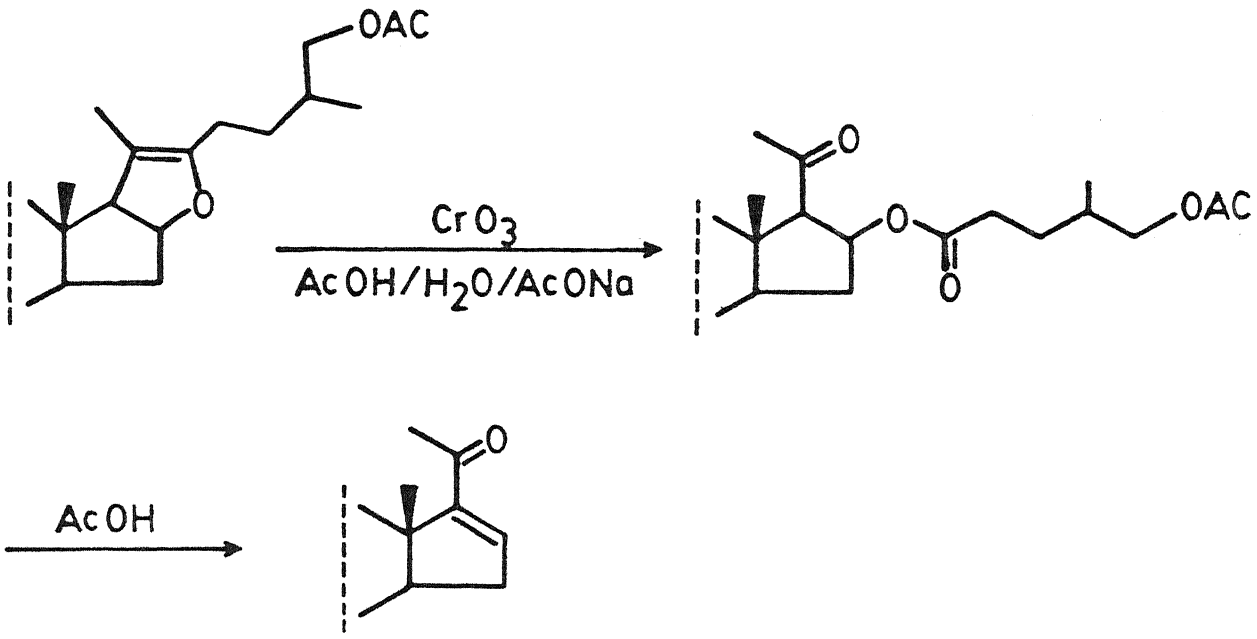
Mechanism:



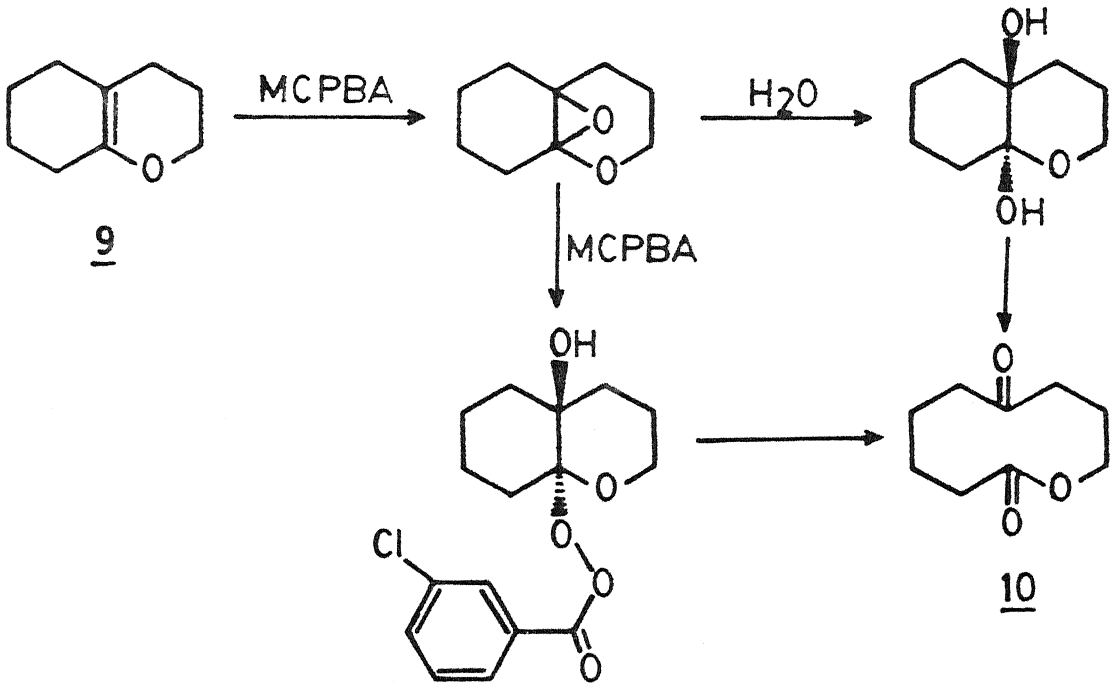
Scheme-IA-1·4



Scheme-IA-1·5



Scheme-IA-1·6



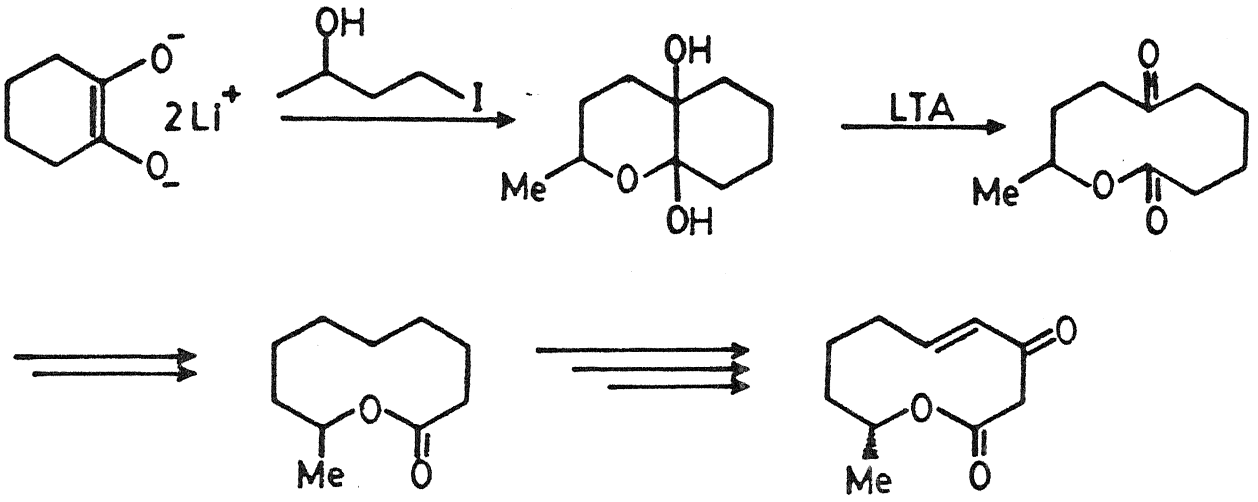
bond formation, (c) ring enlargement and/or fragmentation. One of the most notable and useful developments in this area involves conversion of a bicyclic vinyl ether to a ring-enlarged keto-lactone. The oxidative cleavage of bicyclic enol ether generates a large ring from a bicyclic system and at the same time creates a lactone moiety also.

Borowitz et al.[40] reported the synthesis of several keto lactones of various sizes, ranging from 10-to 16-membered, from the bicyclic enol ethers using excess m-chloroperbenzoic acid. Presence of moisture leads to the formation of trans-glycols in lieu of lactones. The glycol may be further oxidized to the corresponding keto-lactone with lead tetraacetate[41] or m-chloro perbenzoic acid.[40c] These results are rationalized by invoking the formation of an intermediate epoxide, which is regio- and stereo-specifically quenched by excess peracid or water (**Scheme IA.1.6**). The oxidative cleavage of glycol with lead tetra acetate has been successfully applied for the synthesis of Diplodialide A, Diplodialide C, and Decan-9-olide[42] (**Scheme IA.1.7**). Similarly benzo and naphtho keto-lactones[43] and certain resorcylic acid lactones related to zearalanone have been synthesized.

Oxidants other than m-chloroperbenzoic acid include chromic acid (or anhydride),[40c,44] tert.butyl or cumene hydroperoxide in the presence of molybdenum hexacarbonyl,[45] ozone[46] and hydrogen peroxide.[47] RuO_4 has also been used for the cleavage of bicyclic enol ethers, albeit in poor yields.[48]

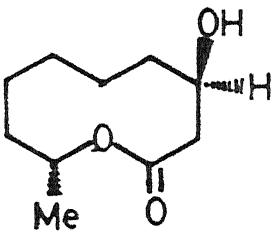
Mahajan et al.[49] developed a new methodology for the

Scheme-IA-1·7



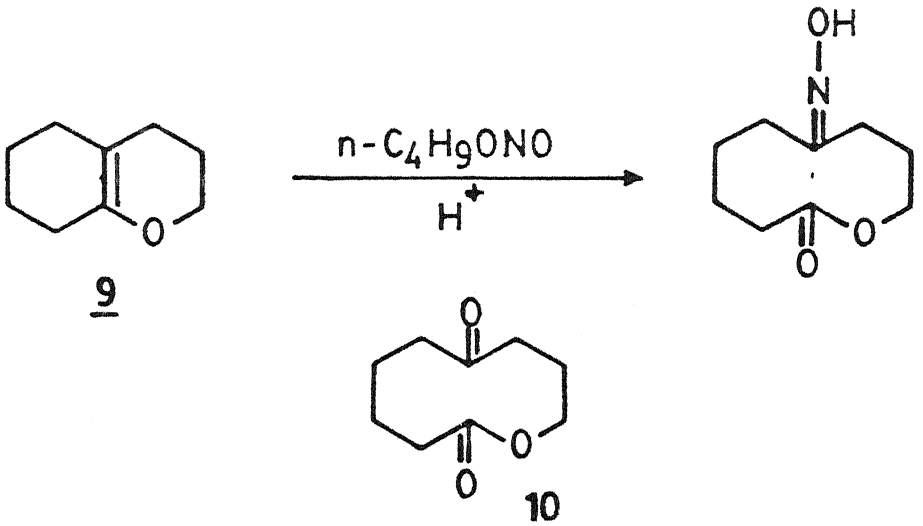
Decan-9-olide

Diplodialide A



Diplodialide C

Scheme-IA-1·8



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cleavage of bicyclic enol ethers to ring enlarged oximino lactones using n-butyl nitrile, which can be converted to the corresponding keto derivatives by hydrolysis[49] or by oxidative deoximation[50] (**Scheme IA.1.8**).

Several group of chemists have also reported[51] the preparation of medium-ring lactones by means of base catalyzed fragmentation of lactols with an electron withdrawing group such as nitro, phenyl sulfonyl, etc. at their angular carbon (**Scheme IA.1.9**).

Recently, synthesis of medium-ring lactones has been reported *via* regio-selective β-session of alkoxyl radicals generated by photolysis of hypoiodite lactols[52] (**Scheme IA.1.10**).

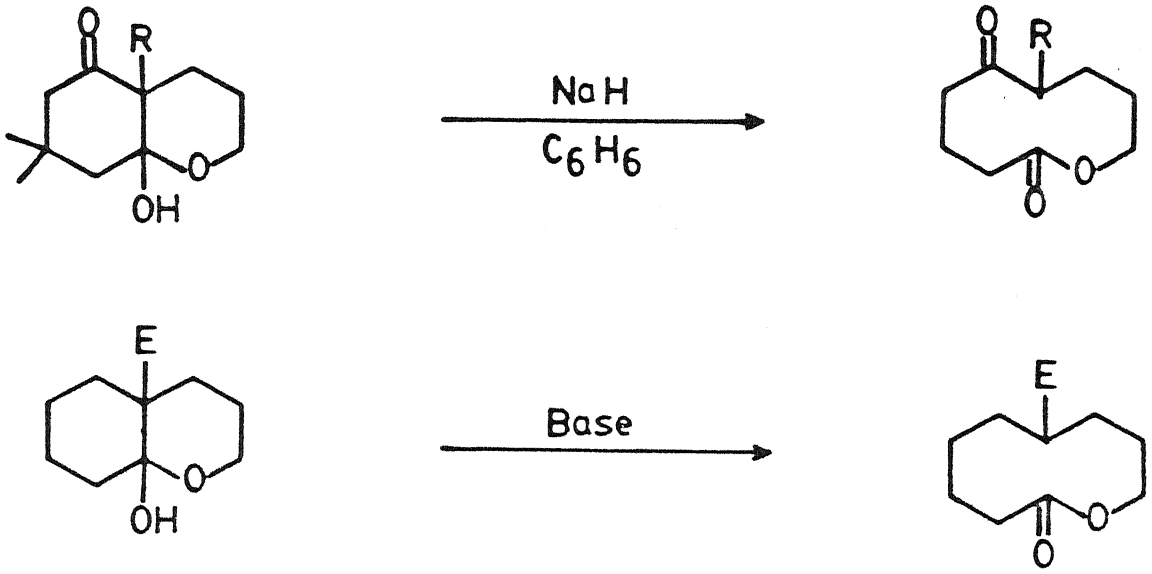
One-pot multicomponent annulations initiated by tributyltin-lithium, followed by oxidative cleavage with lead tetraacetate has been effectively used for the construction of unsaturated macrolides having carbon-carbon double bonds of fixed geometry[39] (**Scheme IA.1.11**).

Recently, Schreiber[53] reported the synthesis of macrolide (±) reciferiolide by treatment of α-alkoxy hydroperoxide with ferrous sulfate/copper acetate. The fragmentation leads to the formation of olefin with fixed regio- and stereochemistry (**Scheme IA.1.12**).

Synthesis of γ-Butyrolactones

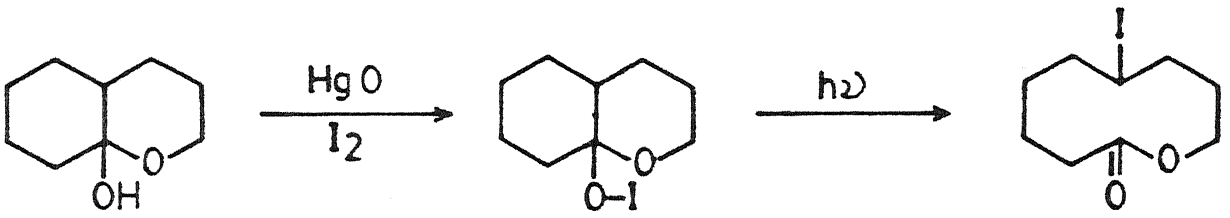
The γ-butyrolactone and α-methylene-γ-butyrolactone structural units have been suggested to be responsible for the bio-

Scheme-IA-1·9

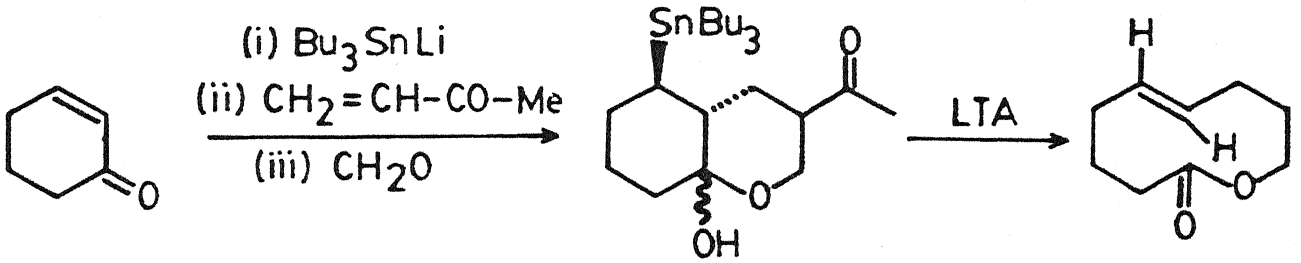


E = NO_2 , $PhSO_2$, CN

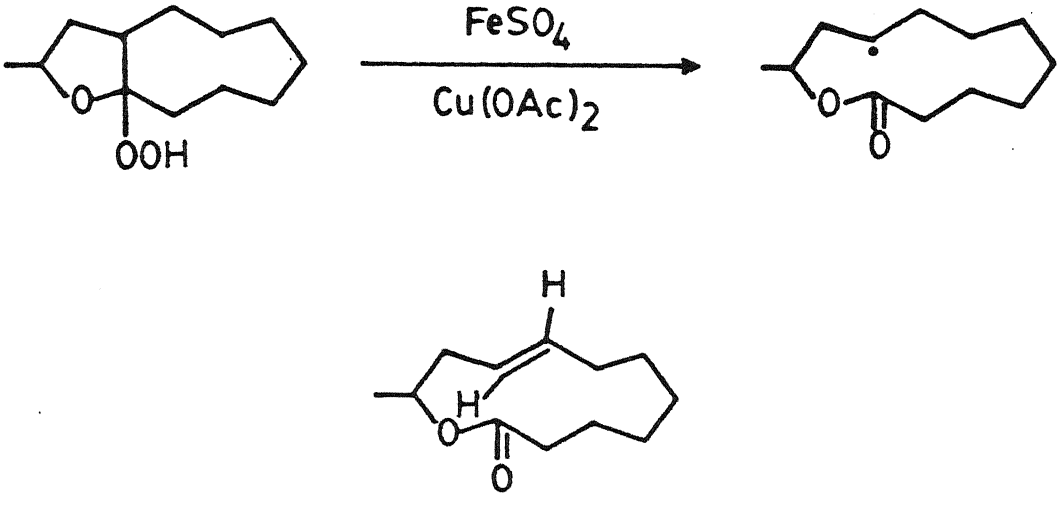
Scheme-IA-1·10



Scheme-IA-1·11

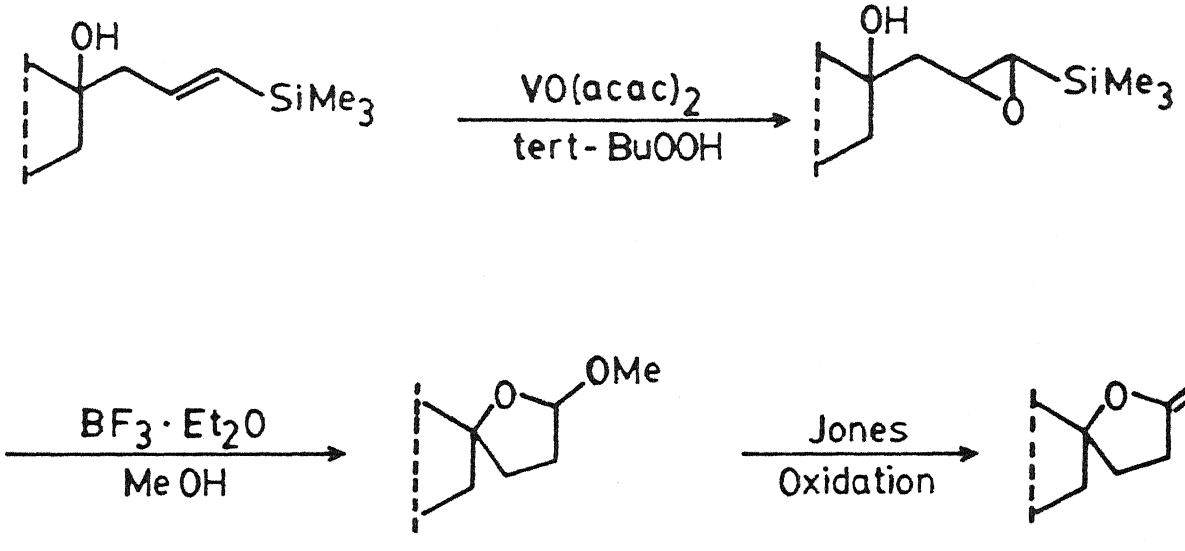


Scheme-IA-1·12



(±) – recifeiolide

Scheme-IA-1·13



logical activity of many natural compounds and their synthetic analogues.[54,55] Since many facile and convenient methods are available for the conversion of γ-butyrolactones to α-methylene-γ-butyrolactones, the chemistry of butanolides has attracted considerable attention of the synthetic chemists.[56] In addition, γ-butyrolactones are versatile starting materials for other important compound classes, e.g., cyclopentenones,[57] furans,[58] etc. In recent years, considerable progress has been made in the development of various procedures for the elaboration of synthetic routes to γ-butyrolactones.[56]

Magnus et al.[59] reported the synthesis of γ-butyrolactones in four steps, which involves δ-hydroxy-α,β-epoxysilane as the key intermediate (**Scheme IA.1.13**).

Recently, Collum et al.[60] reported studies pertaining to mercury-mediated lactonization of cyclopropyl carboxylic acid derivatives.

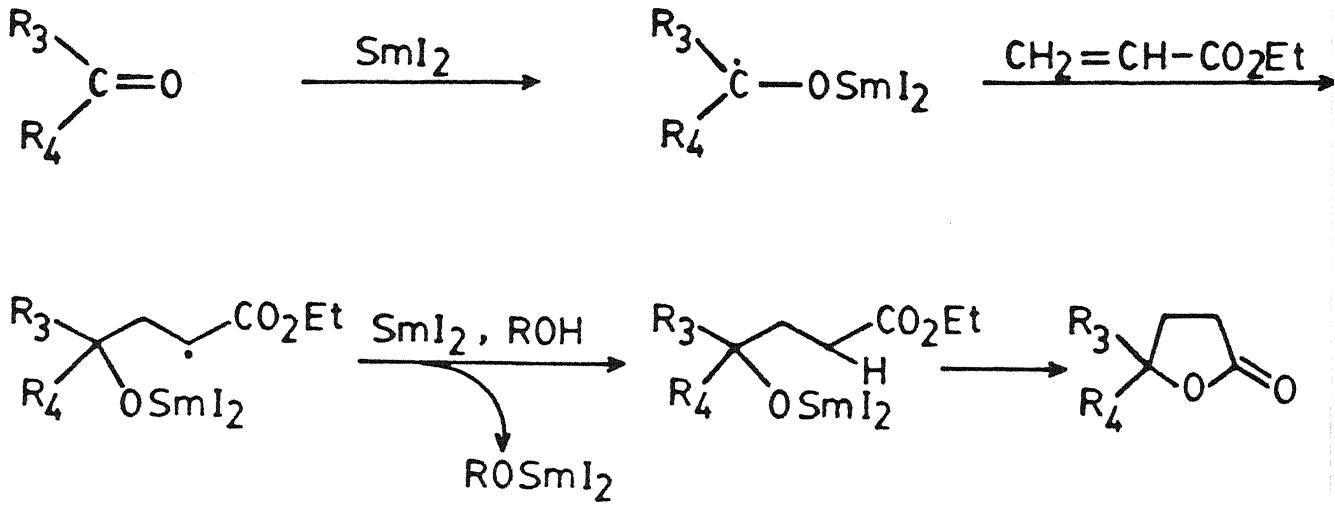
2-Siloxy substituted methylcyclopropane carboxylate has been found to yield γ-butyrolactone on treatment with potassium borohydride in methanol.[56a]

Manganese(III) acetate[61] has been used for the stereo- and regio-specific annulation of γ-lactone rings onto the alkenes.

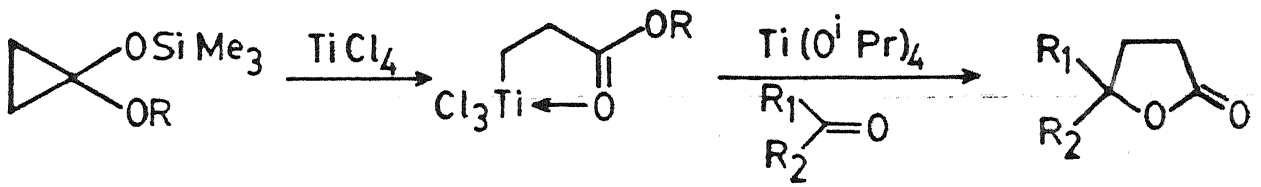
Samarium diiodide promoted [56h] reductive coupling of ketones or aldehydes with electron deficient alkenes,leads to γ-lactones (**Scheme IA.1.14**).

Nakamura et al.[62] reported an extremely efficient method of

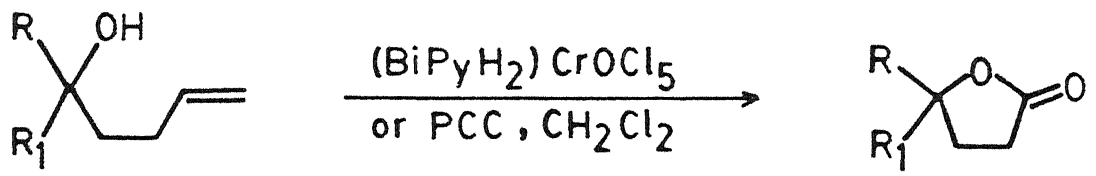
Scheme-IA-1.14



Scheme-IA-1.15

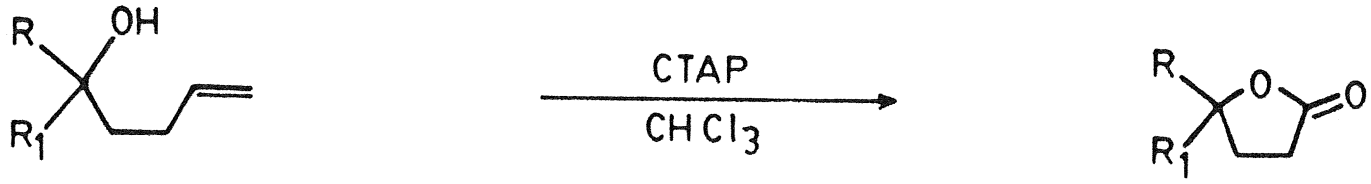


Scheme-IA-1.16



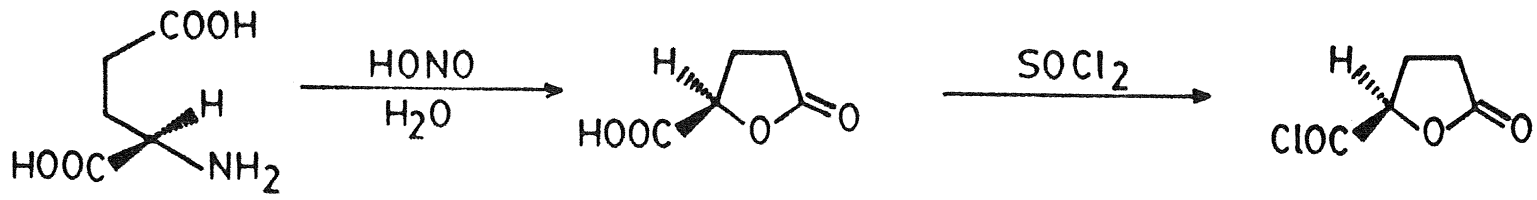
R=R$_1$=-CH$_3$; R=R$_1$ = -(CH$_2$)$_4$- ; R=R$_1$ = -(CH$_2$)$_5$-

Scheme-IA-1·17

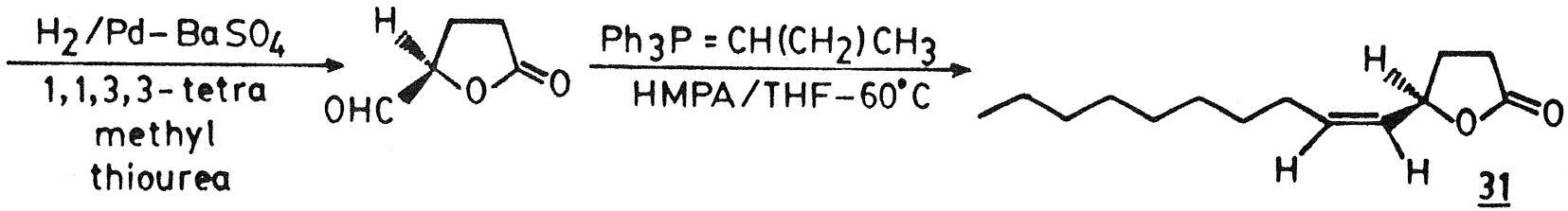


R = R1 = alkyl ; R=H , R1 = alkyl ; R = R1 = H

Scheme-IA-1·18



(R) – Glutamic acid



31

(R,Z)-5-(1-decenyl) oxacyclopentan-2

making γ-lactones by the reaction of titanium homoenolate with aldehydes or ketones (**Scheme IA.1.15**).

Earlier work [63] from our laboratory has shown that the substituent directed oxidative cyclization of tert.hydroxy olefins to lactones by oxo-chromium(VI) reagent, PCC or oxo-chromium(V) reagent, $BiPyH_2CrOCl_5$ (**Scheme IA.1.16**), and more recently cetyltrimethylammonium permanganate has been shown[64] to be an excellent reagent for the oxidative cyclization of primary, secondary and tert-hydroxy olefins to lactones under very mild conditions (**Scheme IA.1.17**).

Even though several methods are available for the construction of γ-lactone ring systems, still there exists a need for the development of complimentary methodology which is chemoselective, inexpensive and convenient to use.

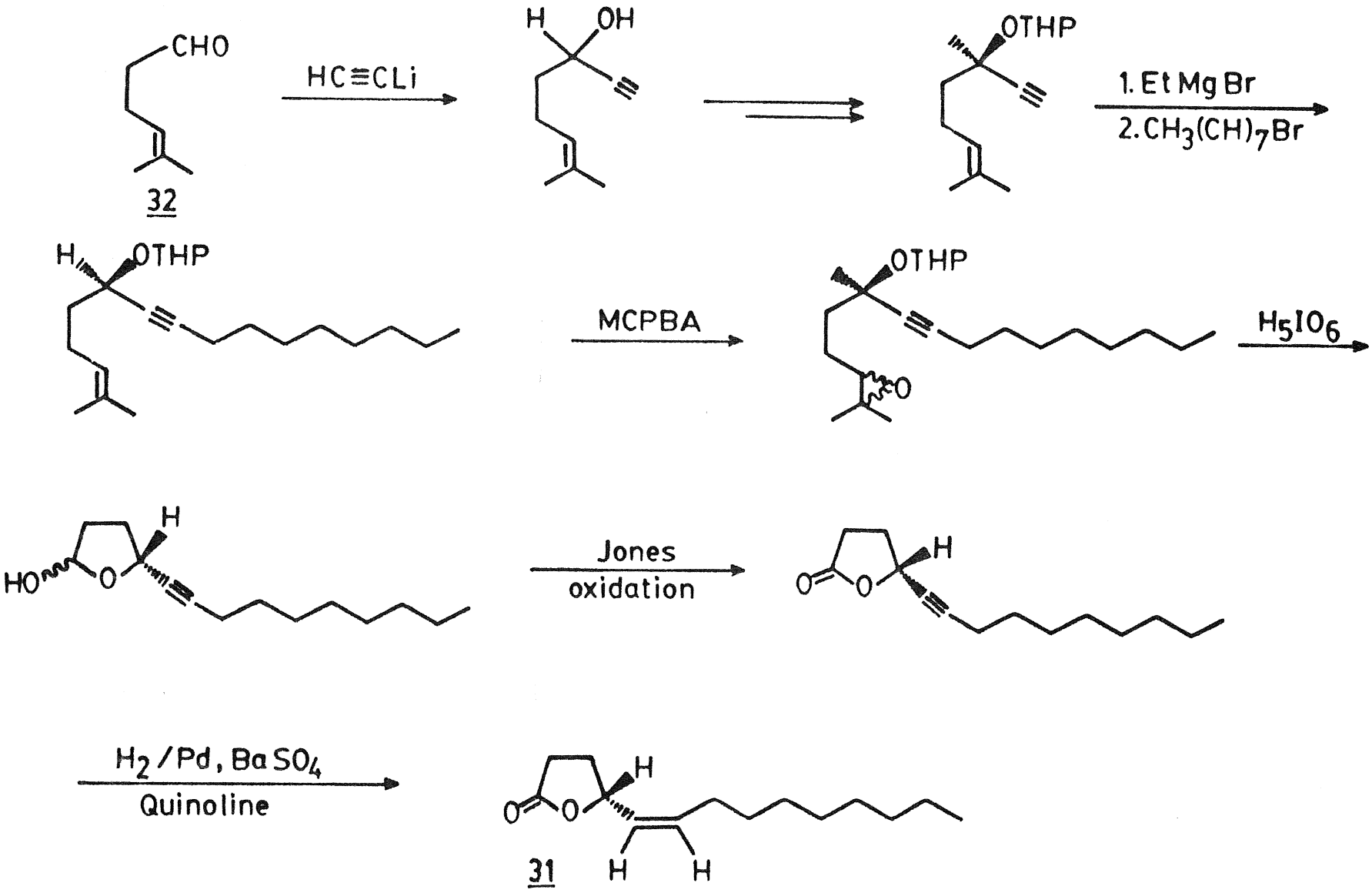
Synthesis of the Sex Pheromone of the Japanese Beetle

The Japanese beetle, Popillia japonica (Japanese name = mamekogane) is a notorious pest in the U.S.A. Its pheromone isolated from virgin females was shown to be (R,Z)-5-(1-decenyl)-oxa cyclopentan-2-one **31** by Tumlinson et al.[65] In their synthetic strategy, they started from (R)-glutamic acid and employed the Wittig reaction to construct the olefinic linkage[65] (**Scheme IA.1.18**).

Mori et al.[66] reported the synthesis, involving lactol as a key intermediate (**Scheme IA.1.19**).

A few more syntheses of chiral as well as racemic mixture

Scheme-IA-1.19



(R,Z)-5-(1-decenyl) oxacyclopentan-2-one

are also available.[67]

The objective of the present study was to develop methods for the selective oxidative cleavage of enol ether double bonds under very mild conditions and explore the synthetic utility of this methodology to the synthesis of Japanese beetle pheromone.

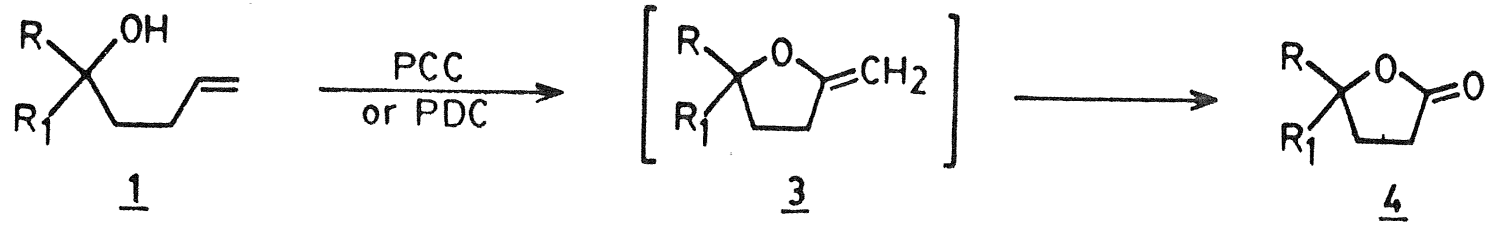
IA.2 RESULTS AND DISCUSSION

In the course of our studies[63] on the substituent directed oxidative cyclization of ω-hydroxy olefins to lactones with oxochromium(VI) reagents like pyridinium chlorochromate (PCC) and pyridinium dichromate (PDC), we believe that the reaction would involve exocyclic enol ether **3** as the key intermediate (**Scheme IA.2.1**).

Piancatelli *et al.*[34] have shown that cyclic and acyclic enol ethers on treatment with pyridinium chlorochromate (PCC) yield lactones and esters, respectively (**Scheme IA.1.5**). This reaction is believed to proceed *via* the formation of a cyclic chromate ester, which decomposes by 1,2-hydride shift to yield the lactone. We anticipated that if the enol ether was highly substituted and devoid of α-vinyl hydrogen for hydride transfer it would behave differently with pyridinium chlorochromate (PCC). Enol ethers of the type **5** would be expected to form the cyclic chromate ester **6** with pyridinium chlorochromate and since there is no possibility for a 1,2-hydride shift, this would undergo an oxidative fragmentation to yield carbonyl compounds **7** and **8** (**Scheme IA.2.2**).

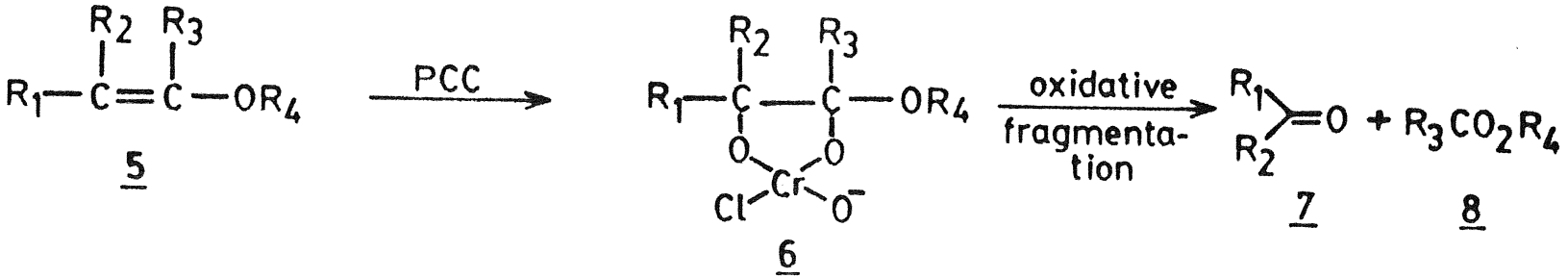
As expected ketone derived enol ethers, **9**, **11**, **13**, **15**, **17**, **19**, **21**, **23** and **25** on treatment with either pyridinium chloro-

Scheme-IA-2·1



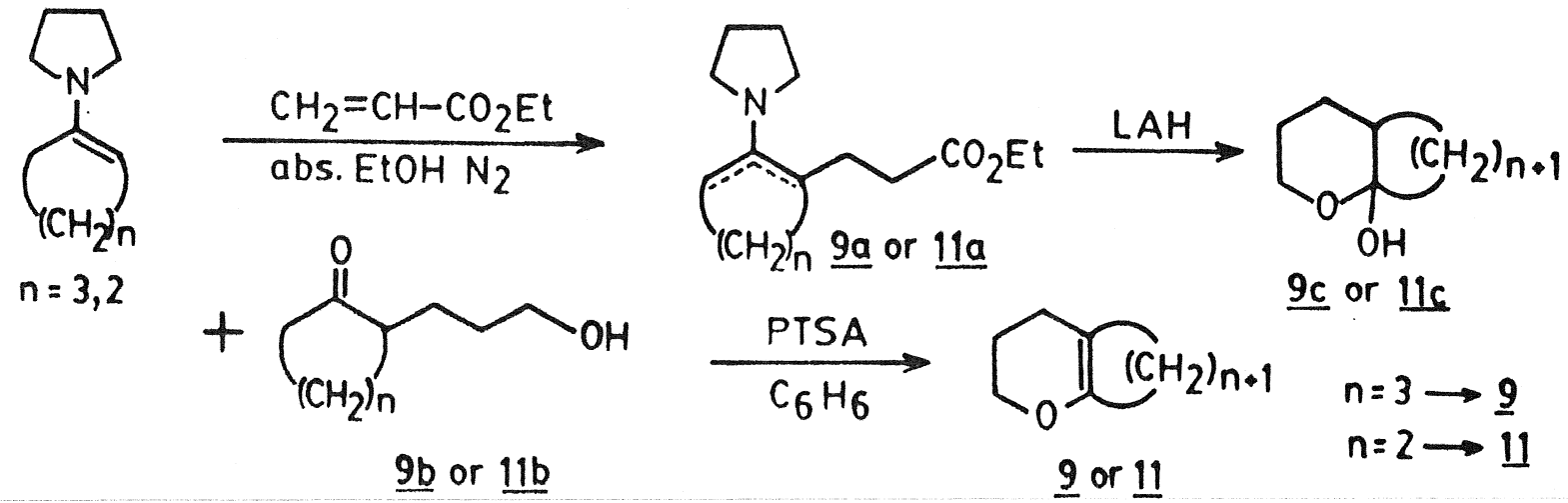
1 3 4

Scheme-IA-2·2



5 6 7 8

Scheme-IA-2·3



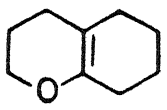
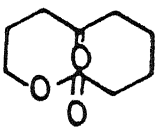
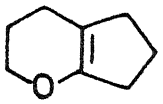
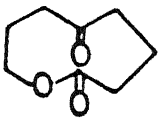
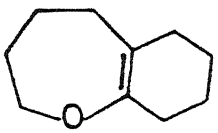
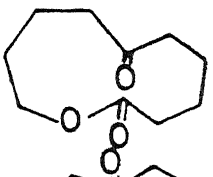
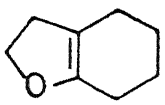
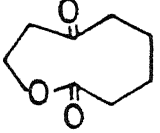
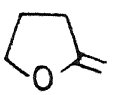
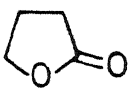
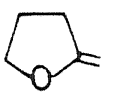
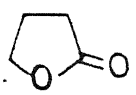
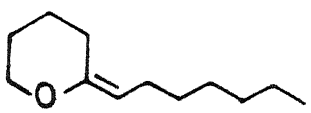
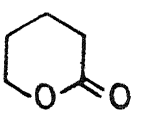
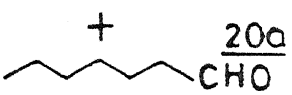
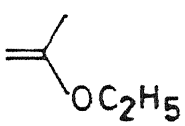
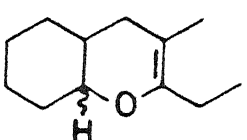
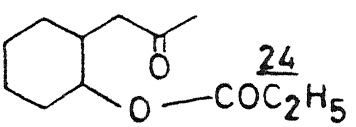
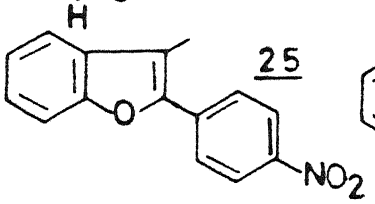
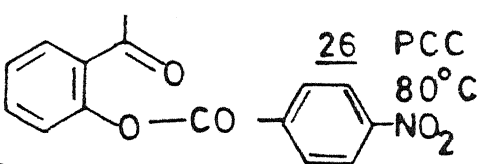
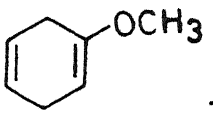
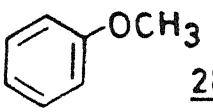
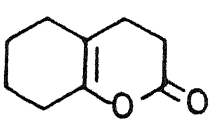
9a or 11a

9c or 11c

9b or 11b

9 or 11

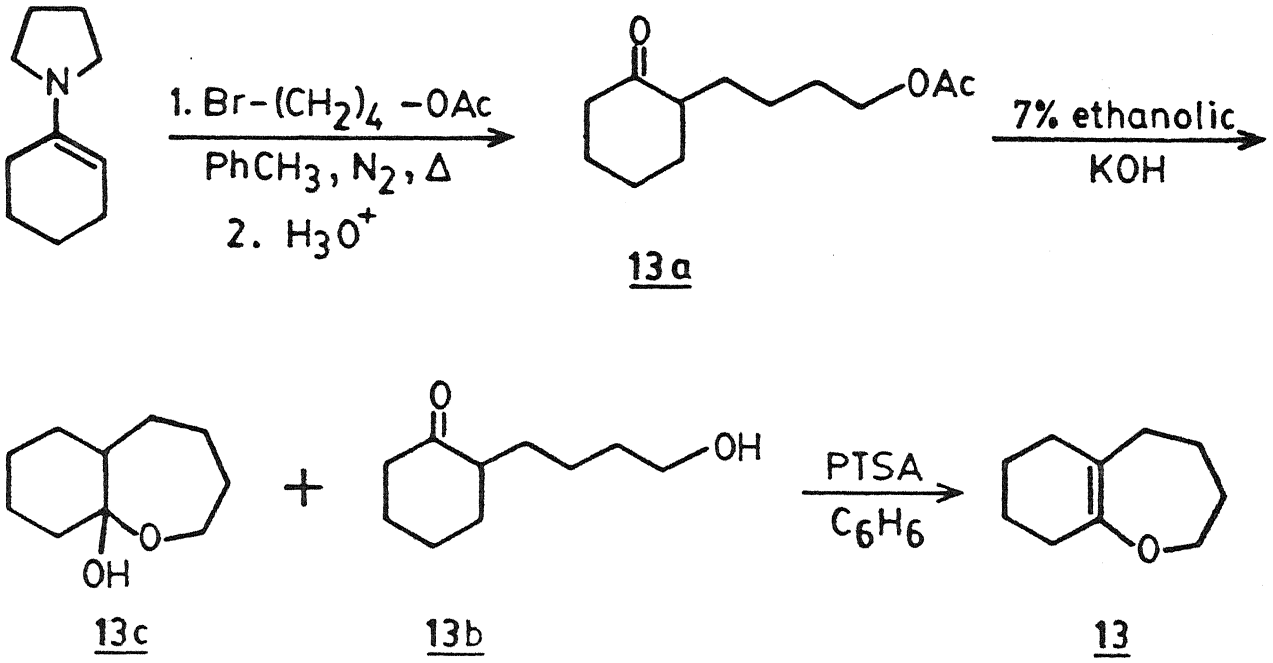
Table-IA-2.1

Entry	Substrate		Product		Reaction Condition	Yield (%)
1		9		10	PCC, CH_2Cl_2 25°C, 1h	85
2		11		12	,,	75
3		13		14	PDC, ϕH 80°C, 4h	64
4		15		16	PCC, CH_2Cl_2 25°C, 1h	63
5		17		18	PCC, ϕH 80°C, 4h	45
6		17		18	PDC, ϕH 80°C, 4h	57
7		19	 + 	20 20a	PCC, CH_2Cl_2 25° C, 2h	62 45
8		21	$CH_3CO_2C_2H_5$	22	,,	65
9		23		24	,,	78
10		25		26	PCC, ϕH 80°C, 4h	70
11		27		28	PCC, CH_2Cl_2 25°C, 1h	100
12		29	—		PCC, ϕH 80°C, 48h	No

chromate (PCC) [4 equiv., 25-80 °C, CH_2Cl_2 or benzene, 1-4 h) or pyridinium dichromate (PDC) (4 equiv., 80 °C, 2-4 h) underwent a smooth oxidative cleavage under mild reaction conditions to afford the carbonyl compounds **10, 12, 14, 16, 18, 20, 22, 24** and **26** respectively in good yield (57-85%) (**Table IA.2.1**).

Compounds **9**[40c] and **11**[49] were prepared by known procedures (**Scheme IA.2.3**). Michael addition of an acrylate ester to a cyclohexanone enamine in absolute ethanol allowed the isolation of the adduct as enamine ester **9a** in 91% yield. The enamine ester was then reduced with lithium aluminum hydride and hydrolyzed to give a mixture of 9-hydroxy hexahydrochroman **9c** and 2-(3'-hydroxy propyl) cyclohexanone **9b**, which was dehydrated to the bicyclic enol ether **9** (88%) via a p-toluenesulfonic acid catalyzed azeotropic removal of water. Bicyclic enol ether **9** underwent a facile oxidative cleavage with pyridinium chlorochromate in dichloromethane to the corresponding keto-lactone **10** in 85% yield. Similarly bicyclic enol ether **11**[49] was prepared from the corresponding cyclopentanone enamine in 84% yield. Bicyclic enol ether **11** was treated with PCC for 1 h, to give the keto-lactone **12** in 75% yield. Alkylation of cyclohexanone enamine with 4-bromobutyl acetate[40c] in acetonitrile gave 2-(4'-acetoxybutyl)cyclohexanone 13a in 22% yield.[40c] Hydrolysis of the ester with ethanolic potassium hydroxide gave a mixture of 2-(4'-hydroxy butyl) cyclohexanone **13b** and its cyclized tautomer **13c**. Azeotropic dehydration of this mixture with p-toluenesulfonic acid in benzene afforded the bicyclic enol ether **13**[40c] (**Scheme IA.2.4**). Bicyclic enol ether **13**, on

Scheme-IA-2·4



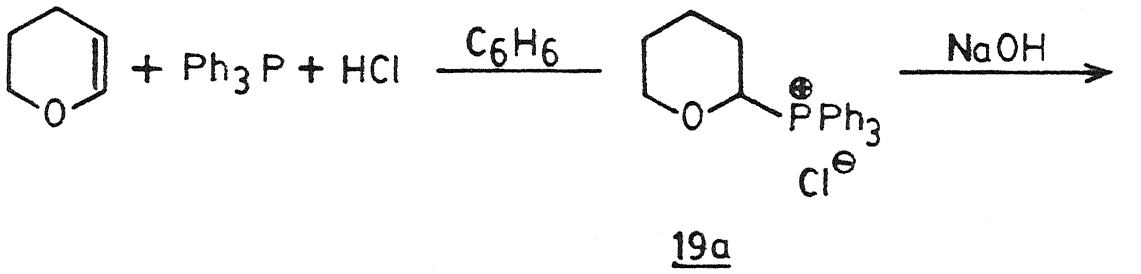
13a

13c

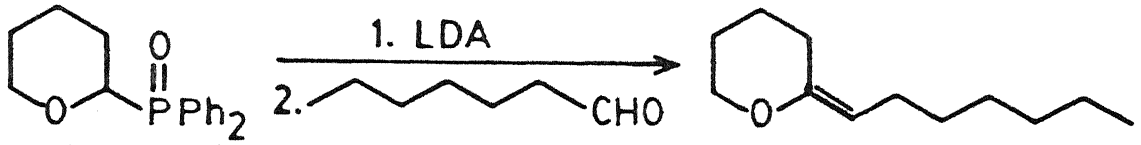
13b

13

Scheme-IA-2·5



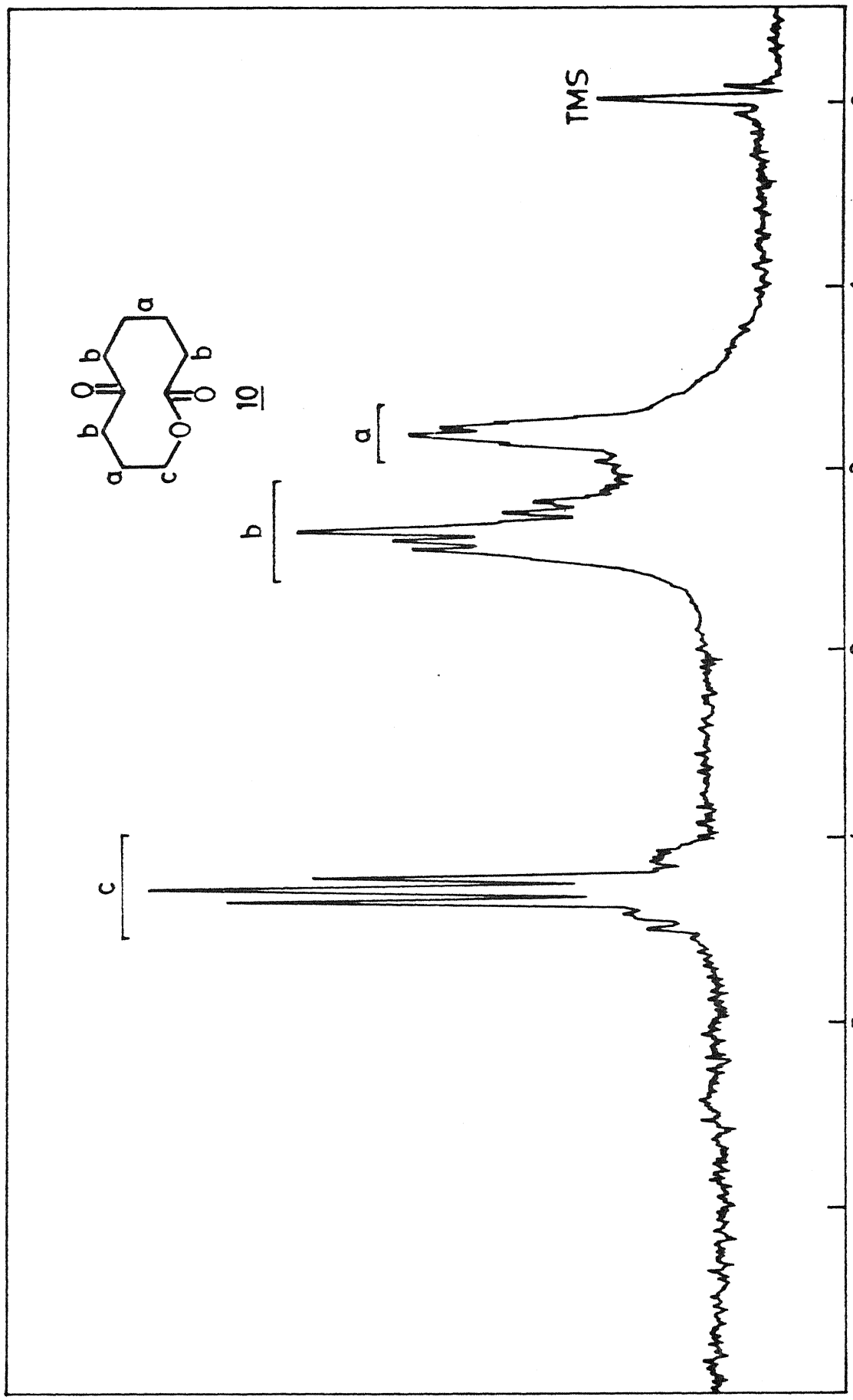
19a



19b

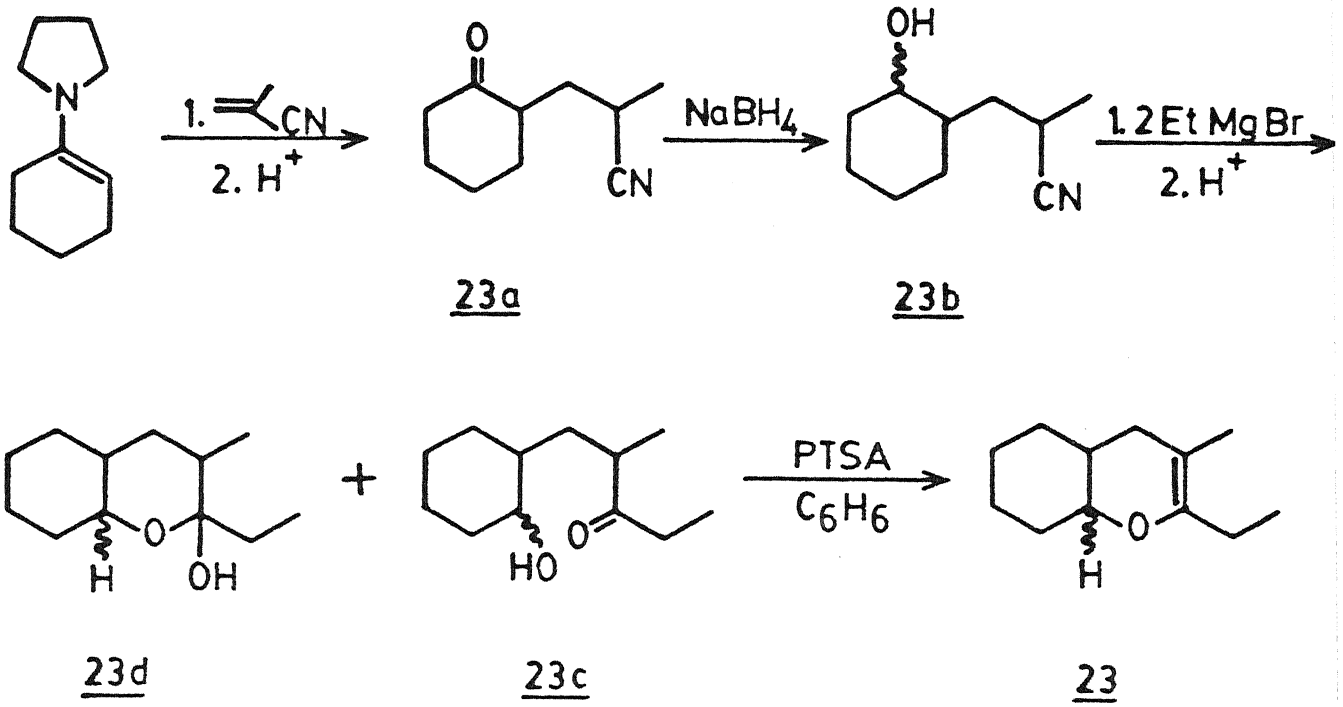
19

treatment with pyridinium dichromate in benzene under reflux for 4 h, yielded the macrocyclic keto-lactone **14** in 64% yield. Enol ether **15** was prepared by the literature procedure.[49] Alkylation of cyclohexanone enamine with ethyl bromo acetate gave **15a**, which on reduction with lithium aluminum hydride followed by dehydration, yielded the desired bicyclic enol ether **15**. Enol ether **15** was allowed to react with pyridinium chlorochromate for 1 h in dichloromethane to give keto-lactone **16** as the only product in 63% yield. Enol ether **17**,[68] prepared from the tetrahydrofurfuryl chloride **17**[69] and solid potassium hydroxide, underwent an oxidative cleavage with pyridinium chlorochromate (PCC) in benzene under reflux for 4 h, to give butyrolactone in 45% yield. Pyridinium dichromate (PDC) in lieu of pyridinium chlorochromate (PCC) gave better result (57%). Enol ether **19**[70] (**Scheme IA.2.5**) when treated with pyridinium chlorochromate, afforded lactone **20** (62%) and heptaldehyde **20a** (45%). Enol ether **21**,[71] prepared from the corresponding 2,2-diethoxy-propane, was oxidatively cleaved with pyridinium chlorochromate (PCC), to give ethyl acetate **22**, which was identified by gas chromatography. Enol ether **23** was prepared by slight modification of the known procedure;[72] alkylation of cyclohexanone enamine with α-methyl acrylonitrile afforded the keto-nitrile **23a**, which was reduced to alcohol **23b** with sodium borohydride, the alcohol **23b** on treatment with 2 equivalents of ethyl magnesium bromide, followed by dehydration yielded the enol ether **23**[72] (**Scheme IA.2.6**). Enol ether **23** was allowed to react with pyridinium chlorochromate (PCC) in dichloromethane for 2 h, to yield keto-ester **24** in 78% yield. Under the

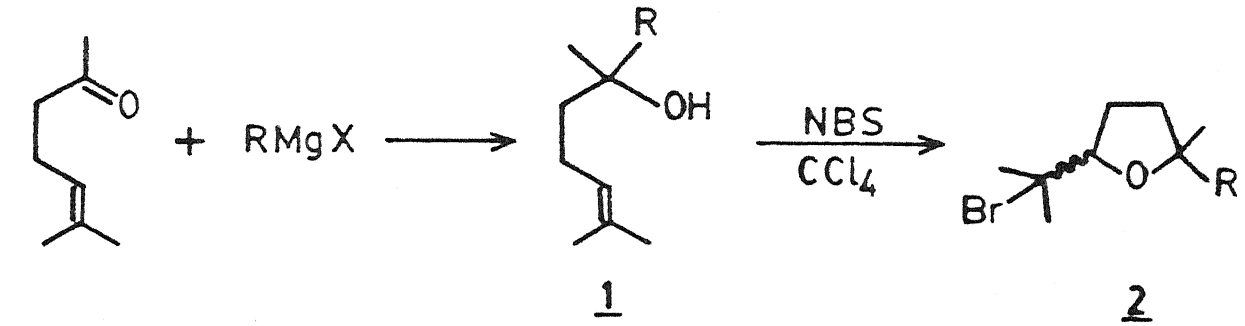


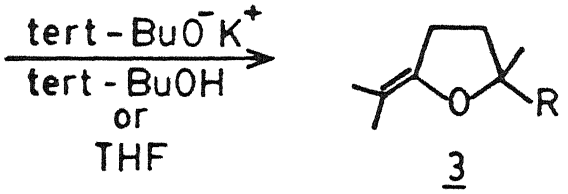
^{1}H NMR Spectrum (80 MHz) of 10

Scheme-IA-2·6



Scheme-IA-2·7





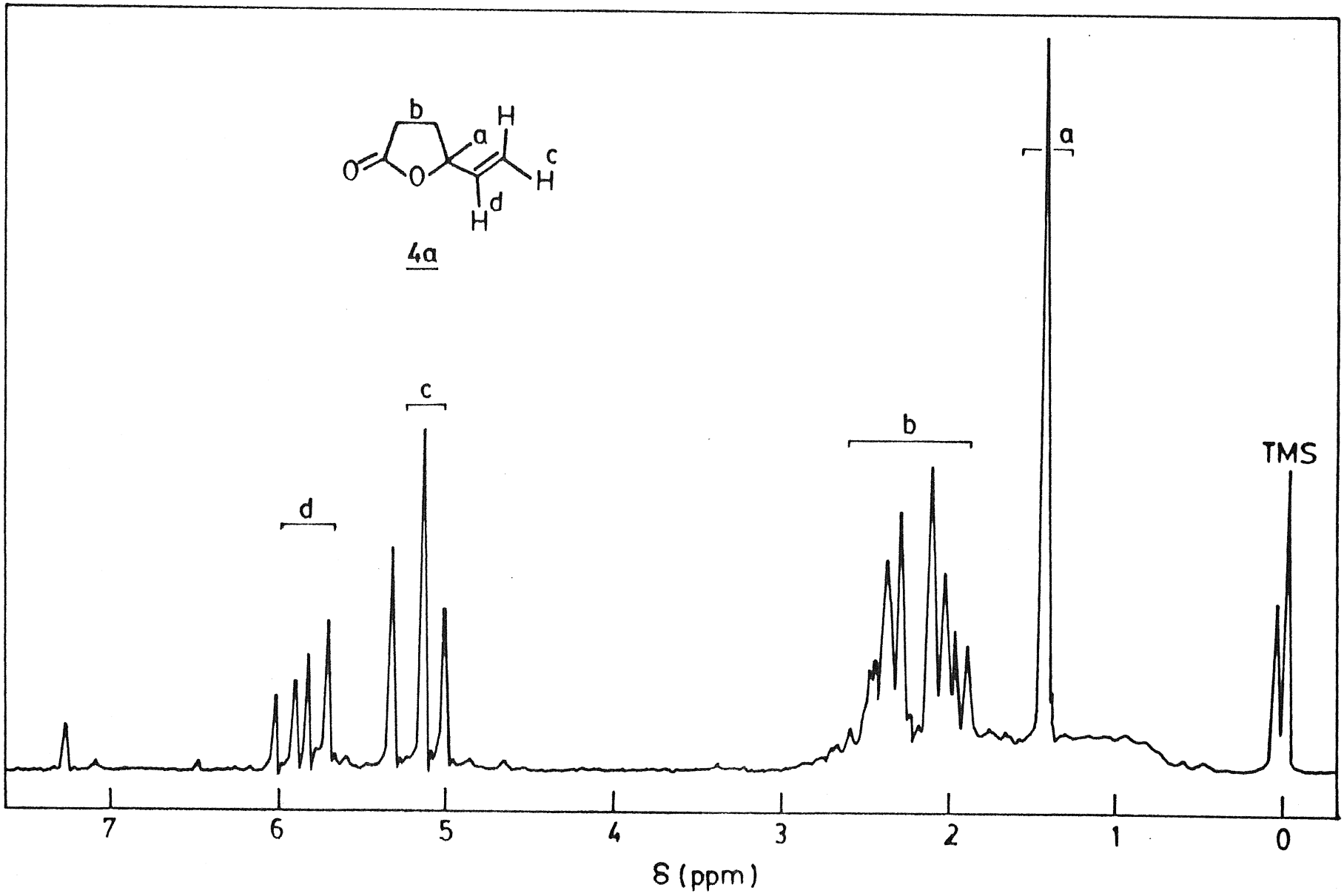
a. R = $-CH=CH_2$
b. R = $-CH_2-CH=CH_2$
c. R = $-C\equiv CH$
d. R = $-C_2H_5$
e. R = $-CH_2Ph$; f. R = $-Ph$; g. R = $-C_6H_{13}$

reaction conditions, with PCC (4 equiv., 80 °C, C_6H_6, 4 h) even benzofuran **25**[73] underwent an oxidative cleavage to compound **26**, albeit slowly. It is interesting to note that PCC at 25 °C induced a facile oxidative aromatization of dihydroanisole **27**[74] to anisole **28** in quantitative yield. Bicyclic enol lactone **29**[75] remained unchanged on treatment with PCC or PDC even after 48 h of refluxing.

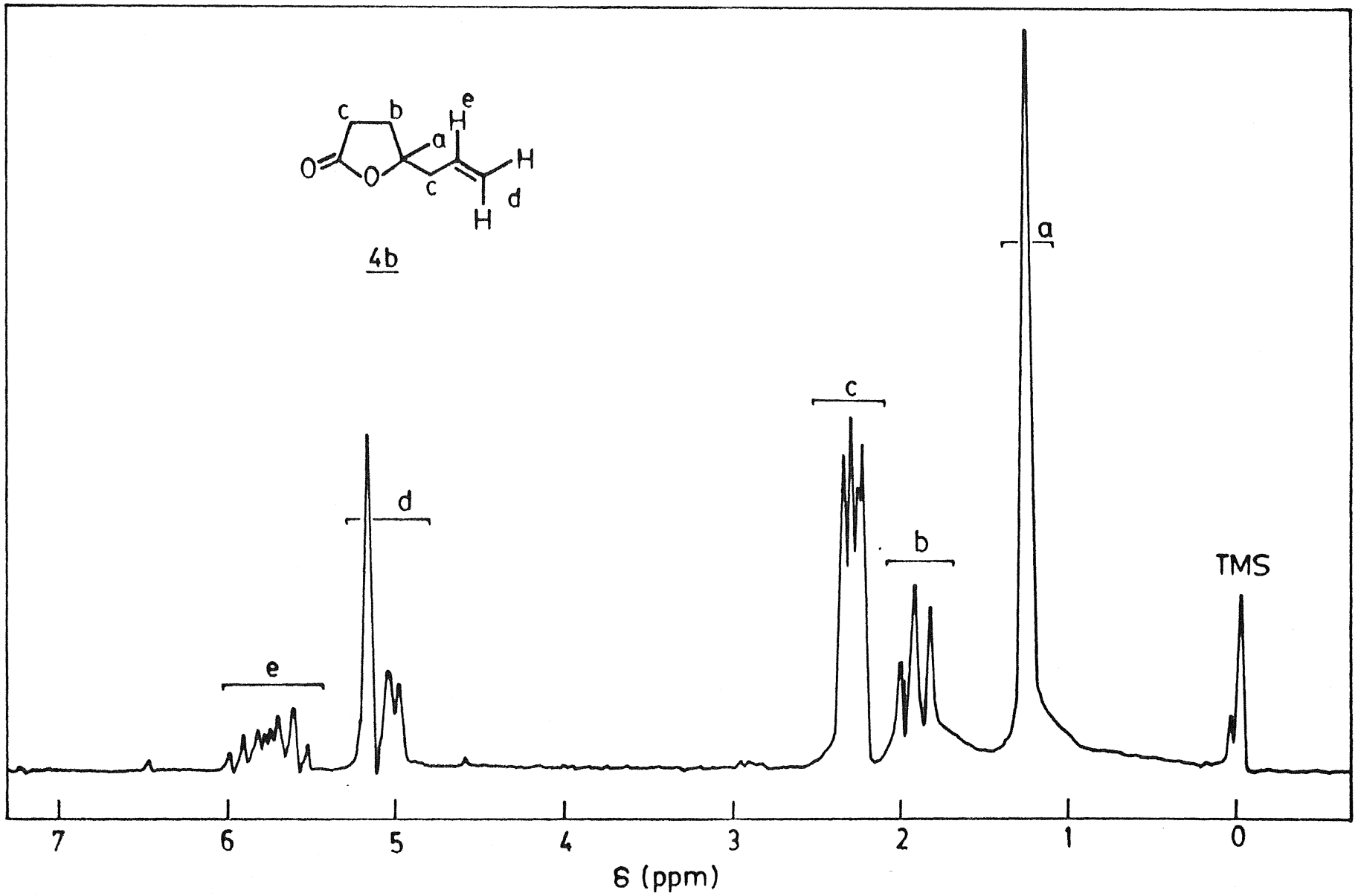
From the afore mentioned experiments, it is very obvious that, oxo-chromium(VI) reagents like pyridinium chlorochromate (PCC) and pyridinium dichromate (PDC) selectively cleave the electron rich double bonds of ketone derived enol ethers to esters, lactones or keto-lactones under mild reaction conditions.

This observation gave us the impetus for further exploration of this methodology in order to expand the scope and utility of this selective transformation in organic synthesis. Accordingly we developed a new and general approach for the synthesis of a variety of substituted butanolides, starting from the readily available carbonyl compounds.

A variety of substituted γ-hydroxy olefins **1** have been converted to butanolides **4** in very high yields in a three step sequence involving haloetherification,[76] elimination and oxidative cleavage. The key step in the overall transformation is the highly selective oxidative cleavage of enol ethers **3** with pyridinium chlorochromate under very mild reaction conditions. Several enol ethers **3a-g** were synthesized adapting a three step strategy (**Scheme IA.2.7**). The first step involved the synthesis



^{1}H NMR Spectrum (90 MHz) of 4a



^{1}H NMR Spectrum (90 MHz) of 4b

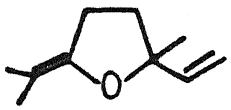
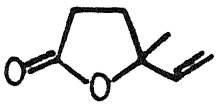
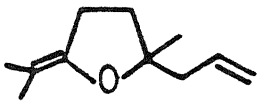
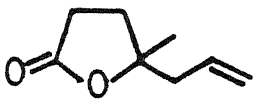
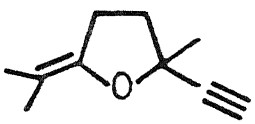
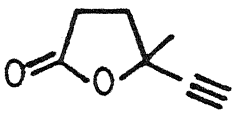
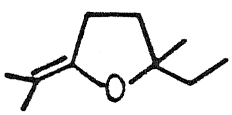
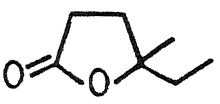
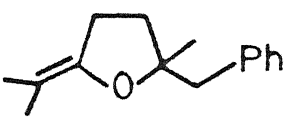
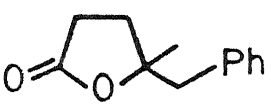
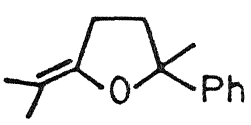
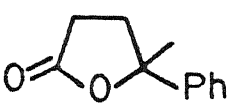
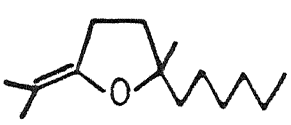
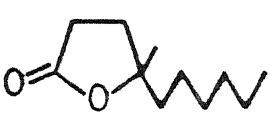
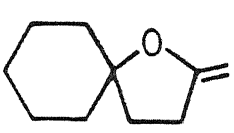
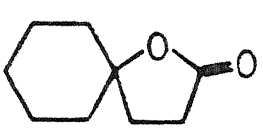
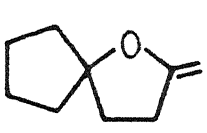
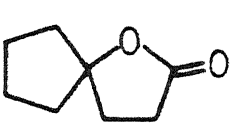
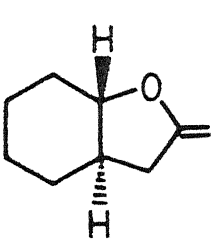
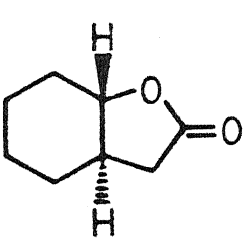
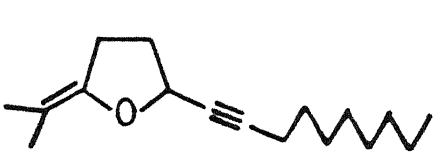
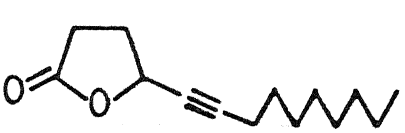
of a number of substituted γ-hydroxy olefins **1a-g** from 6-methyl hept-5-en-2-one **30**[77] by Grignard reaction. The γ-hydroxy olefins **1a-g** were then converted to the corresponding bromo ethers **2a-g** as a mixture of isomers on treatment with N-bromo succinimide at 18-20 ^{o}C.[78] The dehydrobromination[79] was then carried out with potassium tert.butoxide in tert.butyl alcohol or THF and the resulting crude enol ethers **3a-g** were subjected to oxidative fragmentation with pyridinium chlorochromate. By a similar sequence of reactions, enol ethers **3h-i** were prepared from the corresponding carbonyl compounds. trans-2-Allylcyclohexan-1-ol[80] prepared from cyclohexene oxide and allyl magnesium bromide, followed by bromoetherification and elimination with potassium tert.butoxide afforded the enol ether 3j (**Scheme IA.2.8**)

The oxidative cleavage of enol ethers **3a-j** to the corresponding butanolides **4a-j** was effected by treatment with 4 equivalents of PCC at room temperature (28 ^{o}C) for 1-3 h in dichloromethane and proceeded in high yields (**Table IA.2.2**). As can be gauged from **Table IA.2.2**, the key feature of this methodology is that under the reaction conditions other isolated carbon-carbon double bonds and triple bonds, and benzylic groups present in the molecule are not affected.

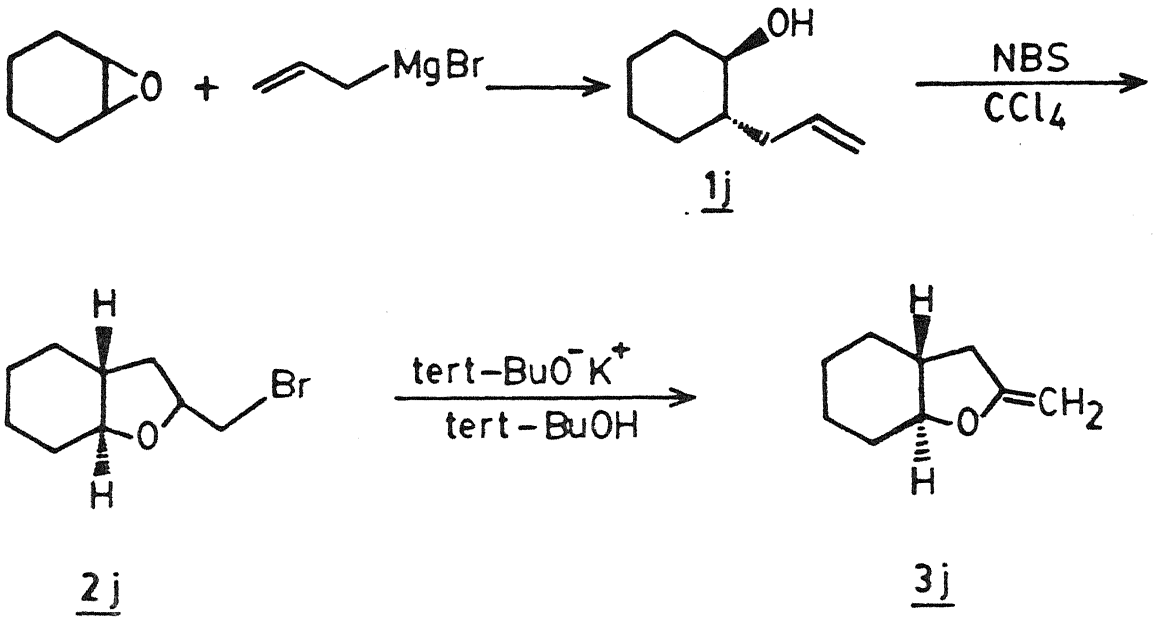
Synthesis of the Pheromone of the Japanese Beetle[65-67]

An application of this general methodology for the synthesis of butanolides has been exemplified in a synthesis of (±) 31, the pheromone component of the Japanese beetle (**Scheme IA.2.9**).[65-67] Enol ether **3k** which is a precursor of **31** was

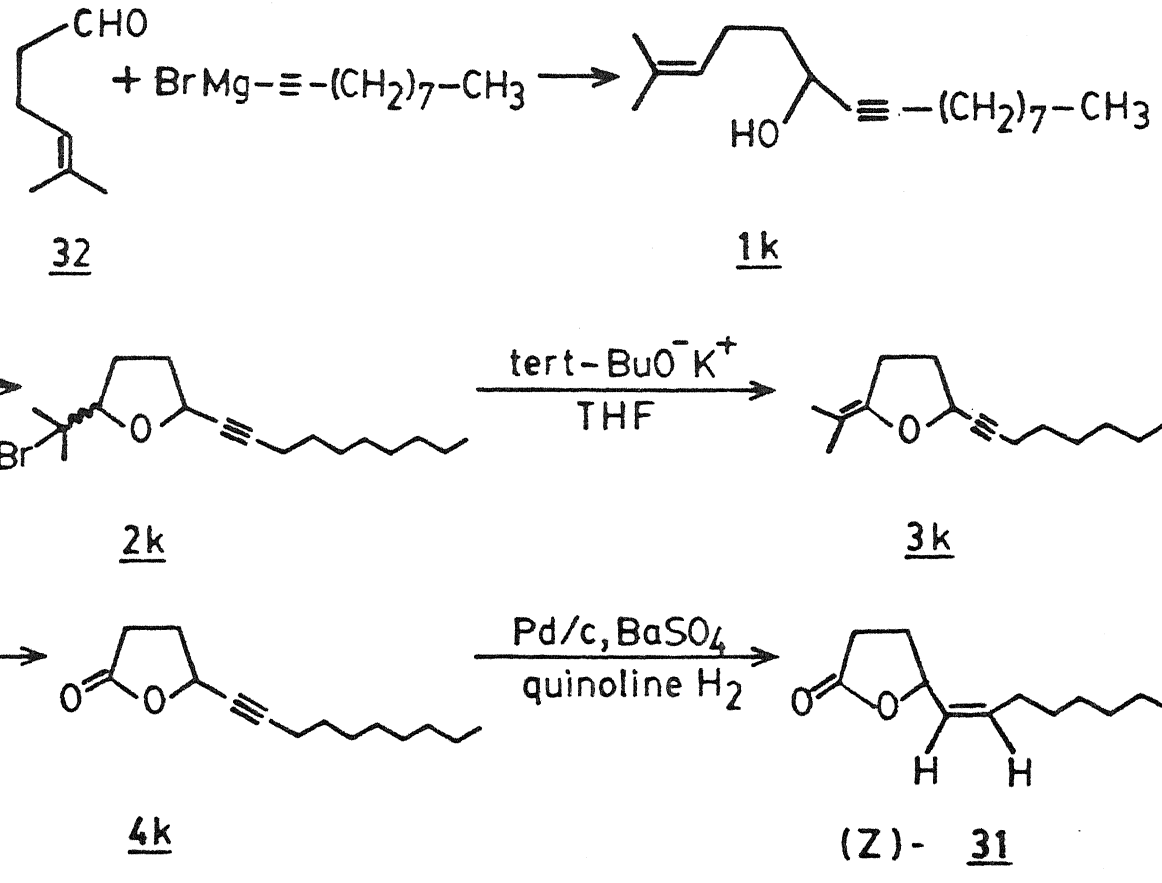
Table-1A-2.2

Y	ENOL ETHER		LACTONE		YIELD(%
		3a		4a	90
		3b		4b	89
		3c		4c	70
		3d		4d	85
		3e		4e	82
		3f		4f	75
		3g		4g	79
		3h		4h	66
		3i		4i	56
		3j		4j	51
		3k		4k	52

Scheme-IA-2·8



Scheme-IA-2·9



synthesized from aldehyde **32**[81] as shown in **Scheme IA.2.9.** Aldehyde **32** was synthesized from 6-methyl hept-5-en-2-one **30**[77] in four steps; haloform reaction, esterification, reduction with lithium aluminum hydride, followed by oxidation with pyridinium chlorochromate. Grignard reagent derived from 1-decyne was allowed to react with aldehyde **32**[81] to yield the alcohol **1k**[66] (58%) which was treated with N-bromosuccinimide in CH_2Cl_2 at 20 °C to afford the bromo ether **2k** (68%) as a mixture of isomers. Dehydrobromination of **2k** was effected by reaction with potassium tert.butoxide in tert.butanol to yield the enol ether **3k**, which was quite unstable. The crude product was immediately treated with 4 equivalents of PCC at room temperature and the γ-lactone **4k**[66] was obtained in 52% yield. Catalytic hydrogenation with Lindlar's catalyst afforded (±) **31**[65-67] (95%) which exhibited spectral data similar to those reported in the literature for the pheromone of the Japanese beetle.[65-67]

IA.3. EXPERIMENTAL

General

All the reactions were performed in oven dried apparatus. Reaction mixtures were stirred magnetically unless otherwise specified. Reaction product solutions were concentrated using a Perfit rotary evaporator and products were characterized by comparison with authentic samples (spectra, tlc, m.p.).

Materials

Commercial grade solvents were distilled prior to use. Benzene was distilled after storing over calcium chloride and kept over sodium wire. Pyridine was distilled over potassium

hydroxide pellets. Chromium trioxide flakes (BDH, E. Merck) was used as such. Petroleum ether fractions 60-80 ^{o}C were used for chromatography.

Chromatography

Analytical thin layer chromatography was performed on Merck precoated glass-backed silica gel 60F-254 0.25 mm plates. Visualization of spots was effected by one or more of the following techniques: (a) Ultraviolet illumination; (b) exposure to iodine vapour; (c) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating to ca. 200 ^{o}C; (d) immersion of the plate in a 3% solution of vanillin in ethanol containing 0.5% concentrated sulfuric acid, followed by heating to dry the plate, and then reimmersion and heating to ca.200 ^{o}C.

Column chromatography was performed using 100-200 mesh Acme silica gel. The flash chromatography was performed using Merck thin-layer chromatography silica gel.

Physical data

Melting points (m.p.) were determined with a Uni-melt capaillary melting point apparatus and are uncorrected. Boiling points (b.p.) are uncorrected.

Infrared (IR) spectra were recorded on Perkin-Elmer model 1320 and 580 spectrophotometers and are reported in wave numbers (cm^{-1}). Proton magnetic resonance (PMR) spectra were recorded at 90 MHz on a Varian EM-390 instrument, at 80 MHz on a Bruker WP-80, at 90 MHz on Jeol Fx-90Q and at 250 MHz on a Bruker Am-250 instrument. Chemical shifts are reported in parts per million

downfield from internal reference tetramethylsilane (TMS) (δ). Multiplicity is indicated using the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), etc. Coupling constants are reported wherever necessary and are expressed in Hz. Mass spectra (MS) were recorded on a Jeol JMS-D 300 mass spectrometer. Principal molecular fragments are reported.

Preparation of Pyridinium Chlorochromate[13]

To hydrochloric acid (6 M, 184 mL, 1.1 mol) was added chromium trioxide (100 g, 1 mol) rapidly with stirring. After five minutes the homogeneous solution was cooled to 0 ^{o}C and pyridine (79.1 g, 1 mol) was carefully added over a period of ten minutes to give a yellow-orange solid, which was collected on a sintered glass funnel and dried for seven hours in a vacuum desiccator to give pyridinium chlorochromate (181 g, 0.84 mol) in 84% yield. The solid is not appreciably hygroscopic and can be stored for extended periods at room temperature without any change.

Preparation of Pyridinium Dichromate[14]

Pyridine (78.83 g, 0.996 mol, 80.6 mL) was gradually added to a cooled solution of chromium trioxide (100 g, 1 mol) in water (100 mL) at below 30 ^{o}C. The solution was diluted with acetone (400 mL) and cooled to -20 ^{o}C to yield orange crystals. The product was collected over a Buchner funnel, washed with cold acetone and dried *in vacuo*, to give pyridinium dichromate (120 g, 0.319 mol) in 64% yield. m.p. 144-146 ^{o}C (lit.[14] m.p. 144-146 ^{o}C)

Preparation of 4-Bromobutyl acetate[40c]

To a mixture of tetrahydrofuran (54 g, 0.75 mol) and zinc chloride (0.02 g) at 0 °C was added acetyl bromide (61.5 g, 0.50 mol) with stirring. The reaction mixture was stirred at 0°C for 0.5 h, allowed to warm to 25 °C over 1 h and then heated at reflux for 0.5 h. After being cooled, chloroform (300 mL) was added, and the organic layer was washed with 100 mL of water, three 50 mL portions of sodium bicarbonate solution and three 100 mL portions of water. The organic layer was dried ($MgSO_4$) and concentrated to yield 88.7 g (91%) of 4-bromo butyl acetate, b.p. 90-93 °C/12 mm (lit.[40c] b.p. 92-93 °C/12 mm).

IR (neat) : 1735 cm^{-1}

^1H NMR (CCl_4) : δ 1.8 (m, 4 H), 1.98 (s, 3 H), 3.48 (t, 2 H), 4.03 (t, 2 H).

Preparation of Pyrrolidine enamine of Cyclohexanone[82]

A solution of cyclohexanone (9.8 g, 0.1 mol), pyrrolidine (11.9 g, 0.167 mol) and catalytic amount of p-toluenesulfonic acid (0.01 g) in dry benzene (60 mL) was refluxed for 6 h with water separation by Dean-Stark apparatus. The benzene and excess pyrrolidine were then removed by distillation at atmospheric pressure and the residue was distilled fractionally under reduced pressure, to get the cyclohexanone enamine[82] (13.89 g, 92%) b.p.112 °C/16-17 mm (lit.[82] b.p.105-107 °C/13 mm).

Alkylation of Cyclohexanone enamine with Ethyl acrylate[40c]

Ethyl acrylate (5.2 g, 52 mmol) in absolute ethanol (10 mL) was added drop wise with stirring to a solution of cyclohexanone enamine (7.10 g, 47 mmol) in absolute ethanol (50 mL) and then

refluxed under nitrogen for 18 h. Absolute ethanol was then distilled off at atmospheric pressure and the residue was distilled under reduced pressure to give enamine ester **9a**[40c] (10.74 g, 91%) b.p. 110-115 °C/0.05 mm (lit.[40c] b.p. 108-115 °C/0.05 mm).

Reduction of Enamine Ester 9a with $LiAlH_4$[40c]

To a slurry of lithium aluminum hydride (0.35 g, 9.2 mmol) in dry tetrahydrofuran (10 mL) was added dropwise with stirring **9a** (2.31 g, 9.2 mmol) in dry tetrahydrofuran (10 mL). After the addition was complete, the mixture was refluxed with stirring for 4 h, cooled to 0 °C with ice and worked up by careful addition of water (0.35 mL), 15% aqueous sodium hydroxide (0.35 mL) and water (1.05 mL), and stirred for an additional 0.25 h. It was filtered through a sintered funnel and washed with ether. The filtrate was washed with 10% hydrochloric acid, aqueous sodium bicarbonate and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to get a mixture of 2-(3'-hydroxypropyl)cyclohexanone **9b** and 9-hydroxy hexahydrochroman **9c** (1.26 g, 88%).

IR (neat) : 3450, 1700 cm^{-1}

Preparation of Tetrahydrochroman 9[40c]

The mixture obtained from the previous step was dissolved in dry benzene (25 mL), p-toluenesulfonic acid (5 mg) was added, and water was azeotropically distilled out during 1.5 h. The benzene solution was washed with sodium bicarbonate solution, dried ($MgSO_4$) and distilled to give tetrahydrochroman **9**[40c] (0.89g,

80%) b.p. 68-72 °C/10 mm (lit.[40c] b.p. 85-100 °C/20 mm).

IR (neat) : 1695 cm^{-1}

^1H NMR ($CDCl_3$) : δ 1.65 (m, 4 H), 1.9 (m, 8 H), 3.95 (t, 2 H).

Oxidation of Enol Ether 9 with PCC

To a stirred mixture of pyridinium chlorochromate (PCC) (1.72 g, 8 mmol) and Celite (1.7 g) in dry dichloromethane (10 mL) was added a solution of enol ether **9** (0.276 g, 2 mmol) in dry dichloromethane (2 mL) at room temperature (28 °C). The reaction mixture was stirred for 1 h and then was diluted with ether (50 mL). After filtering through a pad of Celite and silica gel, the filtrate was evaporated and the residue was purified by flash chromatography on silica gel (elution with 1:3, ethyl acetate-petroleum ether) to afford keto-lactone **10**[41,44a] (0.289 g, 85%) as a white solid m.p. 68-69°C (lit.[44a] m.p. 69.5-71 °C).

IR (CCl_4) : 1710, 1735 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.69-1.70 (m, 6 H), 2.12-2.34 (m, 6 H), 4.33 (t, 2 H).

Preparation of Pyrrolidine enamine of Cyclopentanone[82]

A solution of cyclopentanone (8.4 g, 0.1 mol) pyrrolidine (11.9 g, 0.167 mol) and catalytic amount of p-toluenesulfonic acid (0.01 g) in dry benzene (60 mL) was refluxed for 4.5 h with water separation by Dean-Stark apparatus. The benzene and excess pyrrolidine were then removed by distillation at atmospheric pressure and the residue was distilled fractionally under reduced

pressure, to get cyclopentanone enamine (11.9 g, 87%) b.p. 97-98 ^{o}C/20 mm (lit.[82] b.p. 88-92 ^{o}C/15 mm).

Alkylation of Cyclopentanone enamine with Ethyl acrylate[83a]

To a stirred solution of cyclopentanone enamine (3.22 g, 23.5 mmol) in absolute ethanol (50 mL) was added dropwise ethyl acrylate (2.6 g, 26 mmol) in absolute ethanol (10 mL) and the resulting mixture was refluxed under nitrogen for 18 h. Absolute ethanol was then distilled off at atmospheric pressure and the residue was distilled under reduced pressure to give enamine ester **11a** (4.734 g, 85%) b.p. 112-115 ^{o}C/0.25 mm (lit.[83a] 110-115 ^{o}C/0.25 mm).

Reduction of Enamine Ester 11a with $LiAlH_4$[83a]

To a slurry of lithium aluminum hydride (0.35 g, 9.2 mmol) in dry tetrahydrofuran (10 mL) was added dropwise with stirring **11a** (2.180 g, 9.2 mmol) in dry tetrahydrofuran (10 mL). After the addition was complete the mixture was refluxed with stirring for 4 h, to yield a mixture of 2-(3'-hydroxypropyl)cyclopentanone **11b** and compound **11c** (1.2 g).

IR (neat) : 3460, 1730 cm^{-1}

Preparation of Bicyclic Enol Ether 11[49]

The mixture obtained from the previous step was dissolved in dry benzene (25 mL), p-toluenesulfonic acid (5 mg) was added, and water was azeotropically distilled out during 1.5 h. The benzene solution was washed with aqueous sodium bicarbonate solution, dried ($MgSO_4$), and the solvent was evaporated. The crude product, after chromatographic purification on basic alumina (1:20, ether-petroleum ether) afforded bicyclic enol ether

11[49,83a] (0.958 g, 84%).

IR (neat) : 1695 cm^{-1}

^1H NMR (CCl_4) : δ 1.67-1.96 (m, 6 H), 2.03-2.53 (m, 6 H), 3.8-3.93 (t, 2 H).

Oxidation of Enol Ether 11 with PCC

Enol ether **11** (0.248 g, 2 mmol) was treated with pyridinium chlorochromate (1.72 g, 8 mmol) and Celite (1.7 g) in dry dichloromethane (15 mL) at 28 °C for 1 h to yield keto-lactone **12**[49] (0.234 g, 75%)

IR (neat) : 1735, 1710 cm^{-1}

^1H NMR ($CDCl_3$) : δ 1.67-1.92 (m, 4 H), 2.23-2.46 (m, 6 H), 4.21-4.33 (t, 2 H)

MS (m/e) : 156 (M^+)

Reaction of Cyclohexanone enamine with 4-Bromobutyl acetate[40c]

A mixture of 1-pyrrolidinocyclohexene (15.1 g, 0.1 mol) and 4-bromobutyl acetate (39 g, 0.2 mol) in toluene (100 mL) was heated at reflux for 24h; distilled water (10 mL) was added and heating was continued for another 0.5h. The organic layer was separated, washed with 10% sulfuric acid (2x20 mL) and then with water (3x20 mL) and dried over anhydrous $MgSO_4$, to yield 18.5 g of unreacted 4-bromobutyl acetate, b.p. 90-92 °C (11 mm), and 2-(4'-acetoxy butyl) cyclohexanone **13a**[40c] (4.6g, 22%) b.p. 133-136 °C/0.5 mm (lit.[40c] b.p. 134-135.4 °C/0.5 mm).

IR (neat) : 1740, 1710 cm^{-1}

^1H NMR(CCl_4) : δ 1.2-1.8 (m, 12 H), 1.93 (s, 3 H), 2.1-2.3

(m, 3 H), 3.98 (t, 2 H).

Hydrolysis of 2-(4'-Acetoxybutyl)cyclohexanone[40c]

A solution of **13a** (2.52g, 11.9 mmol) in 7% ethanolic potassium hydroxide [0.7 g, 12.5 mmol of KOH dissolved in 5 mL of water and diluted to 10 mL with ethanol] was kept at room temperature for 24 h. After the solvents were removed in vacuo, the residue was dissolved in water (2.5 mL) and extracted with ether (2x25 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and solvent was evaporated to yield crude 2-(4'-hydroxybutyl)cyclohexanone **13b** and its tautomer **13c**.

The above mixture was dissolved in dry benzene (15 mL), p-toluenesulfonic acid (5 mg) was added and water was azeotropically distilled out during 1 h. The benzene solution was washed with sodium bicarbonate solution, dried ($MgSO_4$) and distilled to give enol ether **13**[40c] (1.39 g, 74%) b.p. 89-91 ^{o}C/11 mm (lit.[40c] b.p. 91-92 ^{o}C/11 mm).

IR (neat) : 1685 cm^{-1}

^{1}H NMR (CCl_4) : δ 1.48-1.66 (m, 8 H), 1.92-2.08 (m, 6 H), 3.78 (t, 2 H).

Oxidation of Enol Ether 13 with PDC

To a stirred mixture of pyridinium dichromate (PDC) (3.0 g, 8 mmol) and Celite (3.0 g) in dry benzene (20 mL) was added a solution of enol ether **13** (0.304 g, 2 mmol) in dry benzene 2 mL) at room temperature. The resulting mixture was stirred under reflux for 4 h and then diluted with ether (50 mL). After filtering through a pad of Celite and silica gel, the filtrate

was evaporated and the residue was purified by flash chromatography on silica gel (elution with ethyl acetate-petroleum ether, 1:10) to yield keto-lactone **14**[40c] (0.236 g, 64%) as an oil.

IR (neat) : 1735, 1715 cm^{-1}

^1H NMR ($CDCl_3$) : δ 1.67-1.84 (m, 8 H), 2.36-2.52 (m, 6 H), 4.02 (t, 2 H).

MS (m/e) : 184 (M^+)

Reaction of Cyclohexanone enamine with Ethyl Bromoacetate[83b,c]

Freshly distilled ethyl bromoacetate (9.185 g, 55 mmol) in dry benzene (10 mL) was added dropwise to a boiling solution of cyclohexanone enamine (7.55 g, 50 mmol) in dry benzene (60 mL). Refluxing was then continued for another 3 h. Solvent and excess ethyl bromo acetate were removed under vacuum and the residue was distilled under reduced pressure to give enamine ester **15a**[83b,c] (8.532 g, 72%) b.p. 125-129 ^oC/0.5 mm (lit.[83b] b.p. 120-123 ^oC/0.45 mm).

Reduction of Enamine Ester 15a with $LiAlH_4$[83b,84]

To a slurry of lithium aluminum hydride (0.38 g, 10 mmol) in dry tetrahydrofuran (10 mL) was added dropwise with stirring **15a** (2.37g, 10 mmol) in dry tetrahydrofuran (10 mL). Once the addition was complete the mixture was refluxed with stirring for 5h. After the usual work-up, a mixture consisting of 2-(2'-hydroxyethyl)cyclohexanone **15b**[83b] and its tautomer **15c**[83b] was obtained.

This mixture was dissolved in dry benzene (15 mL), p-toluene sulfonic acid (5 mg) was added and water was azeotropically

distilled out during 1 h. The benzene solution was washed with sodium bicarbonate solution, dried ($MgSO_4$) and solvent was evaporated. The crude product, after chromatographic purification on basic alumina (eluent: ether-petroleum ether, 1:20) yielded bicyclic enol ether **15**[83b,c] (0.967 g, 78%). b.p. 55-57 ^oC/10 mm (lit.[83c] b.p. 56 ^oC/10 mm)

IR (neat) : 1710, 1440, 1380, 1280, 1260, 1200 cm^{-1}

^1H NMR ($CDCl_3$): δ 1.68-1.89 (m, 4 H), 1.96-2.39 (m, 6 H), 3.23-3.41 (t, 1 H), 4.0 (m, 1 H)

Oxidation of Bicyclic Enol Ether 15 with PCC

A mixture of enol ether **15** (0.248 g, 2 mmol), pyridinium chlorochromate (1.72 g, 8 mmol) and Celite (1.7 g) in dichloromethane (15 mL) was stirred for 1 h to give the keto-lactone **16** (0.197 g, 63%) as an oil after flash chromatography on silica gel (eluent: ethyl acetate-petroleum ether, 1:3).

IR (neat) : 1735, 1710 cm^{-1}

^1H NMR ($CDCl_3$) : δ 1.7-1.93 (m, 4 H), 2.23-2.46 (m,4 H), 2.67-2.83 (t,2 H), 4.47-4.63 (t,2 H).

MS (m/e) : 156 (M^+)

Preparation of Tetrahydrofurfuryl Chloride 17a[69]

In a 250 mL two necked round bottomed flask, fitted with a mechanical stirrer and a dropping funnel, was placed freshly distilled tetrahydrofurfuryl alcohol (15.81 g, 0.155 mol) and pyridine (13.47 g, 0.17 mol). The mixture was cooled in an ice bath and to it was added dropwise with constant stirring freshly distilled thionyl chloride (19.34 g, 0.16 mole). After the

addition of a portion of thionyl chloride, a pasty crystalline mass separated and the temperature began to rise. Addition of thionyl chloride was controlled such that the temperature was not allowed to go beyond 60°C. The solid mass redissolved on addition of the remaining thionyl chloride, ice bath was removed and stirred for 3-4 h. The liquid was extracted with ether and the combined ethereal layers were washed with water and dried over anhydrous $MgSO_4$. The solvent was evaporated and the crude product thus obtained was distilled under vacuum to yield tetrahydrofurfuryl chloride **17a**[69] (13.16 g, 70.5%). b.p. 53-54°C/20 mm (lit.[69] b.p. 41-42°C/11 mm)

Preparation of Tetrahydro-2-methylenefuran 17[68]

To a suspension of powdered potassium hydroxide (5.22 g, 93.2 mmol) in a 25 mL round bottomed flask was added 2-(chloromethyl) tetrahydrofuran **17a** (4.995 g, 41.4 mmol). A fractional distillation assembly was attached with a receiver flask containing few potassium hydroxide pellets and the contents were refluxed for 8 h by maintaining the oil-bath temperature at 120°C. The temperature was gradually increased from 120°C to 180°C, tetrahydro-2-methylene furan **17** started distilling and was collected at 0 °C and was redistilled using a fractionating column to yield **17**[68] (2.787 g, 80%) b.p. 98-99°C (lit.[68] b.p. 98-99°C).

IR (neat) : 3090, 1665, 1175, 1040 cm^{-1}

^1H NMR($CDCl_3$) : δ 1.8-2.2 (m, 2 H), 2.5(m, 2 H), 3.8 (m, 1 H), 4.0, 4.1 (2d, 2 H) 4.1 (m, 1 H).

Oxidation of Tetrahydro-2-methylenefuran 17 with PCC

A mixture of enol ether **17** (0.168 g, 2 mmol) pyridinium chlorochromate (1.72 g, 8 mmol) and Celite (1.7 g) in benzene (15 mL) was refluxed for 4 h. It was then cooled to room temperature, diluted with ether (50 mL) and filtered through a pad of silica gel. The filtrate was concentrated and the residue was purified by flash chromatography on silica gel (1:3, ethyl acetate-petroleum ether) to yield butyrolactone **18** (0.077 g, 45%) as an oil.

IR (neat) : 1775 cm^{-1}

^1H NMR($CDCl_3$) : δ 2.0-2.2 (m, 2 H), 2.3-2.5 (t, 2 H), 4.3-4.4 (t, 2 H).

MS (m/e) : 86 (M^+).

Oxidation of Enol Ether 17 with PDC

Treatment of **17** (0.168 g, 2 mmol) with PDC (3.0 g, 8 mmol), under similar condition, yielded lactone **18** (0.098 g, 57%) after chromatographic purification. Spectral data of this compound were identical with the one obtained by the PCC oxidation of **17**.

Preparation of Tetrahydro-2H-pyran-2-yl Triphenylphosphonium Chloride 19a[70]

2,3-Dihydro-4H-pyran (10.0g, 0.12 mol) was added dropwise to a solution of triphenyl phosphine (30.0 g, 0.115 mol) in dry benzene (250 mL) and dry hydrogen chloride was bubbled through the resulting solution at room temperature for 5 h. The solvent was removed under reduced pressure to give a solid, which could be partially purified by recrystallization from dichloromethane-ethyl acetate to give tetrahydro-2H-pyran-2-yl triphenyl phos-

phonium chloride **19a**[70] (39.5 g, 90%) as a white amorphous solid, m.p. 110-114 °C (lit.[70] m.p. 113-116 °C).

IR ($CHCl_3$) : 3370, 1440, 1110, 690 cm^{-1}

^1H NMR ($CDCl_3$) : δ 1.50-2.20 (m, 6 H), 3.80-4.20 (m, 2 H), 5.85-6.15 (m, 1 H), 7.55-8.00 (m, 15 H).

Preparation of Tetrahydro-2H-pyran-2-yl Diphenyl Phosphine oxide 19b[70]

Phosphonium salt **19a** (36.3 g, 94.9 mmol) was dissolved in 3N aqueous NaOH (180 mL, 540 mmol) and the resulting solution was heated under reflux for 0.5 h. After cooling to room temperature, the mixture was extracted with chloroform (3x100 mL) and the organic extracts were dried over $MgSO_4$ and solvent was removed to give a solid, which was recrystallized from dichloromethane-ethyl acetate to give tetrahydro-2H-pyran-2-yl diphenyl phosphine oxide **19b**[70] (23.0 g, 85%) as a white crystalline solid m.p. 152-154°C (lit.[70] m.p. 154°C).

IR ($CHCl_3$) : 2940, 1435, 1185, 695 cm^{-1}

^1H NMR ($CDCl_3$) : δ 1.30-2.15 (m, 6 H), 3.25-3.6 (m, 1H), 3.90-4.40 (m, 2 H), 7.20-7.60 (m, 6 H), 7.7-8.1 (m, 4 H).

Horner-Wittig Reaction of 19b with Heptaldehyde[70]

A solution of phosphine oxide **19b** (2.86 g, 10 mmol) in dry tetrahydrofuran (10 mL) was added to a stirred solution of LDA [derived from diisopropylamine (1.113 g, 11 mmol) and n-butyl lithium (0.705 g, 11 mmol)] at -78°C. The anion was stirred for 1 h at -78 °C then a solution of n-heptaldehyde **20a** (1.14 g,10 mmol) was added and the reaction mixture was warmed to room

temperature. It was poured into saturated aqueous ammonium chloride solution and extracted with chloroform (3x20 mL). The organic layer was dried over $MgSO_4$ and solvent was evaporated to give a crude product. This was immediately dissolved in dry THF and a solution of tert.BuOK (1.12 g, 10 mmol) in THF was added and stirred at room temperature for 1h. The solvent was removed and the residue was dissolved in dichloromethane. The residue was extracted with ether and filtered through a pad of Celite. The solvent was removed under reduced pressure and the crude mixture on chromatographic purification, on basic alumina, using ether-petroleum ether (1:20), as eluent, gave enol ether **19**[70] (1.27 g, 70%).

IR (neat) : 2940, 1660, 1495, 1050 cm^{-1}

^1H NMR ($CDCl_3$) : δ 0.89 (t,3 H), 1.12-1.36 (m, 10 H), 1.55-1.65 (m, 6 H), 3.85 (m, 2 H), 4.41, 4.84 (2 t, 1H).

Oxidation of Enol Ether 19 with PCC

Enol ether **19** (0.364 g, 2 mmol) in dry dichloromethane (15 mL) was treated with pyridinium chlorochromate (1.72 g, 8 mmol) and Celite (1.7 g) for 2h, to yield heptaldehyde **20a** (0.103 g, 45%) and δ-valerolactone **20** (0.124 g, 62%) after chromatographic purification on silica gel (eluent: ethyl acetate-petroleum ether, 1:5). Heptaldehyde **20a** and lactone **20** were found to be identical in all respect with the authentic samples.

Preparation of 2-Ethoxy-1-propene 21[71]

A mixture of 2,2'-diethoxy propane (13.2 g, 100 mmol), quinoline (1.0 g) and p-toluenesulfonic acid (0.02 g) was

refluxed with slow distillation to yield 2-ethoxy-1-propene **21** (5.16 g, 60%) b.p. 62-63 °C (lit.[71] b.p. 62-63 °C).

IR (neat) : 3090, 1675, 1175-1040 cm^{-1}

^1H NMR ($CDCl_3$) : δ 1.07 (t, 3 H), 1.63 (s, 3 H), 3.53 (q, 2 H), 4.13 (br,s, 2 H).

Oxidation of Enol Ether 21

Enol ether **21** (0.172 g, 2 mmol) in dichloromethane (10 mL) was treated with pyridinium chlorochromate (1.72 g, 8 mmol) and Celite (1.7 g) for 2h. The reaction was monitored by gas chromatography (OV 17 column, N_2 and H_2 50 mL/min, column temp. 60 °C, injection temp. 150 °C, t_R 1.46 min) and showed 65% conversion to ethyl acetate.

Alkylation of Cyclohexanone enamine with α-Methyl acrylonitrile[82]

α-Methyl acrylonitrile (1.61 g, 24 mmol) in absolute ethanol (5 mL) was added dropwise with stirring to a solution of cyclohexanone enamine (3.02 g, 20 mmol) in absolute ethanol (15 mL) and then refluxed under nitrogen for 5 h. Ethanol was then distilled off at atmospheric pressure. The residue was diluted with water (10 mL) and heated on steam bath for 0.5 h. The resulting solution was cooled and extracted with ether. Ether extracts were dried over anhydrous $MgSO_4$ and concentrated to get an oil, which was purified by flash chromatography on silica gel (eluent: ethyl acetate-petroleum ether, 1:2) to afford keto-nitrile **23a** (2.90 g, 88%) as an yellow oil.

IR (neat) : 2230, 1710 cm^{-1}

^1H NMR ($CDCl_3$) : δ 1.36 (d, 3 H), 1.5-1.96 (m, 8 H), 2.01-2.2

(m, 2 H), 2.23-2.42 (m, 2 H).

Reduction of 23a with $NaBH_4$

To a stirred solution of sodium borohydride (0.190 g, 5 mmol) in methanol (10 mL) at $0^{o}C$ was added **23a** (1.65 g, 10 mmol) in methanol (5 mL). The resulting mixture was stirred at room temperature for 1 h. Methanol was removed under vacuum and the residue was extracted with ether (3x15 mL), washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated and the crude product was purified by flash chromatography on silica gel (eluent: ethyl acetate-petroleum ether, 1:1) to afford **23b** (1.637 g, 98%) as a colorless oil.

IR (neat) : 3450, 2230 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 1.23-1.33 (d, 3 H), 1.51-1.92 (m, 11 H) 2.67-3.17 (m, 2 H), 3.43-3.9 (m, 1 H)

Preparation of Enol Ether 23[72]

Ethyl magnesium bromide was prepared from freshly distilled ethyl bromide (1.09 g, 10 mmol) and magnesium turnings (0.24 g, 0.01 g atom) in dry ether (10 mL) under nitrogen. It was then cooled with ice and compound **23b** (0.835 g, 5 mmol) in dry ether (10 mL) was added dropwise with efficient stirring. After the addition was over it was stirred for an additional 3 h at room temperature. Then the reaction mixture was poured slowly, with stirring, into a aqueous ammonium chloride solution and extracted thoroughly with ether. The combined ether extracts were washed with 10% hydrochloric acid (2x10 mL), saturated sodium bicarbonate solution and dried over anhydrous $MgSO_4$. The solvent was evaporated to give a mixture of keto-alcohol **23c** and its

tautomer **23d**.

The above mixture and p-toluenesulfonic acid (5 mg) in dry benzene (15 mL) were heated and water formed in the reaction was removed by azeotropic distillation. The benzene solution was washed with sodium bicarbonate solution, dried ($MgSO_4$) and solvent was evaporated. The crude product after chromatographic purification on basic alumina (eluent: ether-petroleum ether, 1:20) gave enol ether **23** (0.738g, 82%) as a colorless oil.

IR(neat) : 1690 cm^{-1}

^1H NMR($CDCl_3$) : δ 0.83-1.07 (2t, 3 H, two isomers) 1.20-1.33 (m, 9 H) 1.53 (s, 3 H), 1.73-2.17 (m, 4 H), 3.23 and 3.8 (m, 1 H, two isomers).

Oxidation of Enol Ether 23 with PCC

To a stirred mixture of pyridinium chlorochromate (1.72 g, 8 mmol) and Celite (1.7 g) in dry dichloromethane (15 mL) was added enol ether **23** (0.36 g, 2 mmol) at room temperature. The reaction mixture was stirred for 2 h, filtered through a pad of silica gel and purified by flash chromatography on silica gel (eluent: ethyl acetate-petroleum ether, 1:3) to yield keto-ester **24** (0.33 g, 78%) as an oil.

IR(neat) : 1735, 1710 cm^{-1}

^1H NMR ($CDCl_3$) : δ 0.9-1.11 (2t, 3 H), 1.33-1.84 (m, 9 H), 2.01 (s, 3 H), 2.10-2.38 (m, 4 H), 4.33 and 4.91 (m, 1 H).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.92; H, 13.89.

Found : C, 67.96; H, 13.91.

Preparation of 2-p-Nitrophenyl Benzofuran 25[73]

A mixture of 2-hydroxyacetophenone (0.680 g, 5 mmol), 4-nitrobenzyl bromide (1.08 g, 5 mmol) and freshly fused potassium carbonate (0.828 g, 6 mmol) in methanol (10 mL) was refluxed on a steam-bath for 9 h. The reaction mixture was cooled and the precipitate obtained was filtered, washed with methanol and then with distilled water. The product **25** (1.2 g, 95%) was collected and recrystallized from acetic acid. m.p. 138-140 ^{o}C (lit.[73] m.p. 140 ^{o}C)

IR(KBr) : 3090, 3010, 2920, 1640, 1590, 1520 cm^{-1}.

^{1}H NMR($CDCl_3$) : δ 2.6 (s, 3 H), 7.3-7.75 (m, 4 H), 8.0-8.11 (d, 2 H), 8.37-8.48 (d, 2 H).

Oxidation of 2-p-Nitrophenyl Benzofuran 25 with PCC

A mixture of **25** (0.506 g, 2 mmol), pyridinium chlorochromate (1.72 g, 8 mmol) and Celite (1.7 g) in dry benzene (15 mL) was refluxed for 4 h, to yield **26**[85] (0.399 g, 70%) after chromatographic purification on silica gel (eluent: ethyl acetate-petroleum ether 1:3) m.p. 90-91 ^{o}C (lit.[85] m.p. 91-92 ^{o}C).

IR(KBr) : 3090, 3020, 1735, 1680, 1595, 1515 cm^{-1}

^{1}H NMR($CDCl_3$) : δ 2.66 (s, 3 H), 7.27 - 7.73 (m, 4 H), 8.47 (s, 4 H).

Preparation of 1-Methoxy-1,4-cyclohexadiene 27[74]

Lithium metal (0.694g, 100 mmol) was added rapidly with efficient mechanical stirring to redistilled liquid ammonia (80 mL). After stirring for 0.25 h,a solution of anisole (2.16 g, 20 mmol) in dry tetrahydrofuran (15 mL) and absolute ethanol (5 mL)

was added dropwise over 0.25 h. The reaction mixture was stirred for 3h and the excess lithium was carefully destroyed by the addition of solid ammonium chloride. Ammonia was allowed to evaporate, the curdy paste was taken in water and extracted with ether (3x30 mL). The ether extract was washed with brine, dried over $MgSO_4$ and solvent was evaporated to afford a liquid, which was distilled to give a pure 1-methoxy-1,4-cyclohexadiene **27**[74] (1.848 g, 84%) b.p. 146-149 ^{o}C (lit[74] b.p. 148-150 ^{o}C).

Oxidation of Enol Ether 27

A mixture of **27** (0.22 g, 2 mmol), PCC (1.72 g, 8 mmol) and Celite (1.7 g) was stirred for 1 h at room temperature (28 ^{o}C), to yield anisole **28** (0.216 g, 100%), which was found to be identical with an authentic sample.

Oxidation of Enol Lactone 29 with PCC

Enol lactone **29**[75] (0.304 g, 2 mmol), PCC (1.72 g, 8 mmol) and Celite (1.7 g) in dichloromethane were refluxed for 48 h. After the usual work-up, the starting material enol lactone **29**[75] (0.274 g, 90%) was recovered unchanged.

Oxidation of Enol Lactone 29 with PDC

A mixture of **29**[75] (0.304 g, 2 mmol), PDC (3.0 g, 8 mmol) and Celite (3.0 g) in benzene was refluxed for 48 h. After the usual work-up, the starting material enol lactone **29**[75] (0.286 g, 94%) was recovered unchanged.

Preparation of 6-Methyl-hept-5-en-2-one 30[77]

A mixture of citral (66 g), potassium carbonate (70 g) and distilled water (700 mL) was refluxed for 48 h and then the reaction mixture was allowed to come to room temperature. The

organic layer was separated, dried over anhydrous $MgSO_4$ and distilled under reduced pressure to yield 6-methyl-hept-5-en-2-one **30**[77] (42 g, 72%) b,p. 73 °C/ 18 mm (lit.[77] b.p. 58 °C/12 mm).

IR(neat) : 1710, 1640 cm^{-1}

^1H NMR ($CDCl_3$) : δ 1.6-1.7 (d, 6 H), 2.03 (s, 3 H) 2.1-2.5 (m, 4 H), 4.8-5.2(m, 1 H).

Preparation of 32[81]: Haloform Reaction on 30

To a solution of NaOH (42.0 g, 1.05 mol) in distilled water (360 mL) at -5 °C, bromine (43.0 g, 0.263 mol) was added dropwise with stirring. To this reaction mixture at 0 °C was added dropwise a cold solution of **30** (10.1 g, 80 mmol) in dioxane (200 mL). After the addition of **30** was over, the reaction mixture was stirred for 1 h at 0 °C and then for 2 h at room temperature. The excess sodium hypobromite was destroyed by the addition of a solution of sodium sulfite (10 g) in water (100 mL) and dioxane was distilled out. The reaction mixture was then cooled to 0 °C, acidified with conc. HCl (50 mL) and extracted with dichloromethane (3x100 mL). The combined extracts were washed with sodium bicarbonate solution, brine and dried over $MgSO_4$. The solvent was removed to give crude acid **32a**[86] (3.3 g), which on treatment with conc. H_2SO_4 (400 µL) in dry methanol (20 mL) for 24 h at 28 °C, yielded the ester **32b** (2.73 g, 24%) after chromatographic purification on silica gel (eluent: ether-petroleum ether, 1:5) b.p. 58-60 °C/12 mm (lit.[86] b.p. 60-61 °C/12 mm)

IR(neat) : 1735, 1640 cm^{-1}

^{1}H NMR($CDCl_3$) : δ 1.62 (s, 3 H), 1.68 (s, 3 H), 2.30-2.42 (m, 4 H), 3.68 (s, 3 H), 5.11-5.19 (t, 1 H).

$LiAlH_4$ Reduction of Ester 32b

To a slurry of lithium aluminum hydride (0.76g, 20 mmol) in dry tetrahydrofuran (15 mL) was added a solution of **32b** (2.84 g, 20 mmol) in THF (15 mL) and the reaction mixture was stirred under reflux for 3h. After the usual work-up, the crude product was purified by flash chromatography on silica gel (eluent: ether-petroleum ether, 1:5) to yield the alcohol **32c**[86] (2.12 g, 93%) b.p. 82-83 °C/20 mm (lit.[86] b.p. 39-40 °C/0.2 mm).

IR (neat) : 3360, 1640 cm^{-1}

^{1}H NMR ($CDCl_3$) : 1.6 (s, 3 H), 1.68 (s,3 H), 1.74-2.09 (m,5 H), 3.55-3.69 (t ,2 H), 5.12-5.2 (t, 1 H).

Oxidation of alcohol 32c with PCC :

A mixture of pyridinium chlorochromate (4.3 g, 20 mmol) and Celite (4.3) in dichloromethane (30 mL) was treated with **32c** (1.14 g, 10 mmol) in dichloromethane (5 mL) for 1 h at 28 °C. The reaction mixture was diluted with ether (70 mL) and filtered through a pad of silica gel and Celite and the filter cake was washed thoroughly with ether. The filtrate was concentrated to yield the aldehyde **32**[81] (0.762 g, 68%) which was used as such in the next step.

IR (neat) : 2720, 1710, 1640 cm^{-1}

^{1}H NMR ($CDCl_3$) : δ 1.6-1.7 (d, 6 H), 2.03-2.38 (m, 4 H), 4.8-5.2 (m, 1 H), 9.4 (s, 1 H).

4,8-Dimethyl-1,7-nonadiene-4-ol, 1b[87]

A solution of 6-methyl-5-hepten-2-one **30**[77] (2.52 g, 20 mmol) in 15 mL of dry ether was added under nitrogen atmosphere to a solution of allyl magnesium bromide [prepared from magnesium powder (0.528 g, 22 mg atom) and allyl bromide (2.42 g, 20 mmol)] in 30 mL of dry ether over a period of 0.25 h and was stirred at room temperature (28 ^{o}C) for additional 2 h. Saturated NH_4Cl solution (15 mL) was added to the reaction mixture, the organic layer was separated and the aqueous phase was extracted with ether (2x50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent was removed to afford the alcohol **1b**[87] (2.35 g, 70%) as a colorless oil, after chromatographic purification on silica gel [1:9 ethylaceate: petroleum ether (60-80 ^{o}C)].

IR (neat) : 3450, 3080, 1635 cm^{-1}.

^{1}H NMR (CCl_4) : δ 1.16 (s, 3 H), 1.3-1.70 (m, 3 H), 1.72 (s, 3 H), 1.76 (s, 3 H), 2.06-2.2 (m, 4 H), 4.86-5.15 (m, 3 H), 5.6-6.2 (m, 1 H).

3,7-Dimethyl-6-octen-3-ol, 1d[88]

Ethyl magnesium bromide [prepared from ethyl bromide (2.18 g, 20 mmol) and magnesium powder (0.528 g, 22 mg atom)] was allowed to react with **30** (2.52 g, 20 mmol) in ether (30 mL) for 2 h and **1d**[88] (1.014 g, 65%) was obtained as a colorless oil.

IR (neat) : 3460 cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ 0.70-0.93 (t, 3 H), 1.16 (s, 3 H), 1.2-1.29 (m, 1 H), 1.44-1.54 (m, 4 H), 1.63 (s, 3 H), 1.69

(s, 3 H), 1.98-2.08 (q, 2 H), 5.10-5.16 (t,1 H).

1-Phenyl-2,6-dimethyl-5-hepten-2-ol, 1e

Grignard reagent derived from benzyl bromide (1.71 g, 10 mmol) and magnesium powder (0.264 g, 11 mg atom) in ether 30 mL was allowed to react with **30** (1.26 g, 10 mmol) at room temperature for 2 h. Alcohol **1e** was obtained after chromatographic purification as an oil (1.286 g, 59%).

IR (neat) : 3460, 3080, 3050, 3020, 1590 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.12 (s, 3 H), 1.23-1.6 (m, 3 H), 1.62 (s, 3 H), 1.68 (s, 3 H), 2.0-2.26 (m, 2 H), 2.73 (s, 2 H), 5.12 (t, 1 H, J = 6 Hz), 7.2-7.5 (m, 5 H).

Anal. Calcd for $C_{15}H_{22}O$: C, 82.56; H, 10.09.
Found: C, 82.79; H, 10.41.

2-Phenyl-6-methyl-5-hepten-2-ol, 1f[89]

Phenylmagnesium bromide prepared from magnesium powder (0.264 g, 11 mg atom) and bromobenzene (1.57 g, 10 mmol) in ether 30 mL was treated with **30** (1.26 g, 10 mmol) as above for 2.5 h. The alcohol **1f**[89] was obtained as a colorless oil (1.49 g, 73%), b.p. 94 °C/1 mm (lit.[89] b.p. 70 °C/0.1 mm).

IR (neat) : 3380, 3080, 3050, 3020, 1590 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.48 (s, 3 H), 1.54 (s, 3 H), 1.65 (s, 3 H), 1.73- 2.06 (m, 5 H), 5.06 (m, 1 H), 7.19-7.59 (m, 5 H).

2,6-Dimethyl-2-dodecen-6-ol, 1g[88b]

Hexylmagnesium bromide obtained from hexyl bromide (1.65 g, 10 mmol) and magnesium powder (0.264 g, 11 mg atom) in ether 30 mL was reacted with **30** (1.26 g, 10 mmol) as above for 3 h. Alcohol **1g** was obtained as a colorless liquid (1.42 g, 67%) after distillation; b.p. 106-108 ^{o}C/0.3 mm (lit.[88b] b.p. 106-110^{o}C/0.3 mm).

IR (neat) : 3400 cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ 0.89 (t, 3 H), 1.17 (s, 3 H), 1.29 (br,s, 10 H), 1.44-1.50 (m, 3 H), 1.63 (s, 3 H), 1.70 (s, 3 H), 2.01-2.05 (m, 2 H), 5.13 (t, 1 H, J = 6 Hz).

1-(3-Butenyl)Cyclohexan-1-ol, 1h[90]

3-Butenyl magnesium bromide derived from magnesium powder (0.528 g, 22 mg atom) and 3-butenyl bromide (2.7 g, 20 mmol), in 30 mL of dry ether was treated with cyclohexanone (1.96 g, 20 m mol) at room temperature for 2 h. Alcohol **1h**[90] was obtained after chromatographic purification as an oil (1.6 g, 52%).

IR (neat) : 3400, 3080, 1640 cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ 1.3-1.7 (m, 12 H), 2-2.3 (m, 3 H), 4.85-5.2 (m, 2 H), 5.5-6.15 (m, 1 H).

1-(3-butenyl)Cyclopentan-1-ol 1i[90]

3-Butenyl magnesium bromide prepared from magnesium powder (0.528 g, 22 mg atom) and 3-butenyl bromide (2.7 g, 20 mmol) in 30 mL of dry ether was allowed to react with cyclopentanone (1.68

g, 20 mmol) as above for 2 h. Alcohol **1i**[90] was obtained as a colorless liquid (1.4 g, 50%) after distillation; b.p. 62-65 $^{o}C/3$ mm (lit[90] b.p. 62-64 $^{o}C/3$ mm).

IR (neat) : 3400, 3080, 1640 cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ 1.4-1.8 (m, 10 H), 2.05-2.35 (m, 3 H), 4.85-5.2 (m, 2 H), 5.6-6.15 (m, 1 H).

trans-2-(2-propenyl)Cyclohexanol **1j**[80]

Allyl magnesium bromide obtained from allyl bromide (9.1 g, 75 mmol) and magnesium powder (3.65 g, 150 mmol) in ether (60 mL) was treated with cyclohexene oxide (2.45 g, 25 mmol) and the resulting mixture was refluxed for 14 h. Alcohol **1j**[80] was obtained as a colorless liquid (3.325 g, 95%); b.p. 86-88 $^{o}C/23$ mm Hg (lit.[80] 86-88 $^{o}C/23$ mm Hg).

IR (neat) : 3450, 3100, 1650, 1000, 910 cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ 0.8-2.1 (m, 10 H), 2.3-2.7 (m, 1 H), 2.9-3.4 (m, 1 H), 3.5 (s, 1 H), 4.8-5.3 (m, 2 H), 5.4-6.2 (m, 1 H).

2-Methyl hexadec-2-en-7-yn-6-ol **1k**[66]

To a stirred solution of ethyl magnesium bromide prepared from freshly distilled ethyl bromide (0.545 g, 5 mmol) and magnesium powder (0.122 g, 5 mg atom) in 10 mL of dry ether under N_2 at 0 ^{o}C was added 1-decyne (0.690 g, 5 mmol) in THF (5 mL). After the addition was over the reaction mixture was heated under reflux for 2 h. It was cooled to 0 ^{o}C and the aldehyde

Found: C, 51.72; H, 7.42.

Bromoether 2b: The alcohol **1b** (1.68 g, 10 mmol) in 15 mL of dry CCl_4 at 20 °C was treated as above with N-bromosuccinimide (1.958 g, 11 mmol) for 16 h to give the bromoether **2b** (mixture of isomers) (1.86 g, 75%) as a pale yellow oil.

IR (neat) : 3070, 1640 cm^{-1}.

^1H NMR (CCl_4): δ 1.16 (s, 3 H), 1.26-1.60 (m, 2 H), 1.63, 1.67 (2s, 6 H), 1.73-2.03 (m, 2 H), 2.16-2.23 (d, 2 H, J = 7.5 Hz), 3.82 and 4.21 (2t, 1 H, J = 6 Hz), 4.62-5.1 (m, 2 H), 5.5-6.0 (m, 1 H).

MS (m/e): 246, 248 (M^+).

Anal. Calcd for $C_{11}H_{19}BrO$: C, 53.44; H, 7.76.

Found: C, 53.94; H, 7.84.

Bromoether 2c:[78b] Alcohol **1c** (1.30 g, 10 mmol) upon treatment with N-bromosuccinimide (1.958 g, 11 mmol) under similar conditions yielded bromoether **2c**[78b] (1.547 g, 67%) after purification by flash chromatography as a colorless oil.

IR (neat) : 3300, 2100, 1460-1440, 1380, 1370, 1130-980 cm^{-1}.

^1H NMR (CCl_4) : δ 1.47 (s, 3 H), 1.7 (s, 3 H), 1.76 (s, 3 H), 1.8-2.16 (m, 4 H), 2.23 (s, 1 H), 4.01-4.20 (m, 1 H).

MS (m/e) : 215, 217 (M^+-15).

Anal. Calcd for $C_{10}H_{15}BrO$: C, 51.96; H, 6.55.

Found: C, 52.23; H, 6.63.

Bromoether 2d: Bromoether **2d** (mixture of isomers) (1.80 g, 76%) was obtained as a colorless oil on treatment of alcohol **1d** (1.56 g, 10 mmol) with N-bromosuccinimide (1.95 g, 11 mmol) for 18 h

at 20 °C.

IR (neat) : 2980, 2960, 2940, 1465, 1455, 1370, 1130-1020 cm^{-1}.

^1H NMR (CCl_4) : δ 0.87 (t, 3 H), 1.06, 1.11 (2 s, 3 H), 1.20-1.56 (m, 2 H), 1.63 (s, 3 H), 1.67 (s, 3 H), 1.73-2.31 (m, 4 H), 3.70-3.80 (2 t, 1 H).

MS (m/e) : 234, 236 (M^+).

Anal. Calcd for $C_{10}H_{19}BrO$: C, 51.06; H, 8.16.
Found: C, 51.23; H, 8.21.

Bromoether 2e: Alchol **1e** (1.09 g, 5 mmol) under conditions described earlier was reacted with N-bromo succinimide (0.89 g, 5 mmol) in CCl_4 yielded **2e** (1.19 g, 80%) as a colorless oil.

IR (neat) : 3080, 3050, 3020, 1600, 1490, 1440, 1360, 1120-1020, 760, 700 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.26 (s, 3 H), 1.36-1.47 (m, 2 H), 1.73 (s, 6 H) 1.84-2.0 (m, 2 H), 2.96 (s, 2 H), 3.7-3.9 (m, 1 H 7.3 (s, 5 H).

MS (m/e): 297, 299 ($M^+ + 1$).

Anal. Calcd for $C_{15}H_{21}BrO$: C, 60.60; H, 7.13.
Found: C, 60.93; H, 7.20.

Bromoether 2f: Alcohol **1f** (1.02 g, 5 mmol) was treated with NBS (0.89 g, 5 mmol) in CCl_4 under similar conditions as described earlier gave **2f** (mixture of isomers) (1.07 g, 76%) after chromatographic purification.

IR (neat) : 3070, 3060, 1600, 1495, 1445, 1380, 1320, 1130-1030, 760, 700 cm^{-1}.

^{1}H NMR (CCl_4) : δ 1.28-1.4 (m, 2 H), 1.50 (br,s, 3 H), 1.71 (s, 3 H) 1.80 (s, 3 H), 2.12-2.28 (m, 2 H), 3.86-4.20 (m, 1 H), 7.1-7.6 (m, 5 H).

MS (m/e) : 267, 269 (M^+ - 15).

Anal. Calcd for $C_{14}H_{19}BrO$: C, 59.36; H, 6.77.

Found: C, 59.72; H, 6.82.

Bromoether 2g: Alcohol **1g** (2.12 g, 10 mmol) and NBS (1.968 g, 11 mmol) in CCl_4 was stirred at 20 °C gave the bromoether (mixture of isomers) **2g** (2.33 g, 80%) as an oil after chromatographic purification.

IR (neat) : 2980, 2940, 2870, 1455, 1370, 1020, 860 cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ 0.89 (t, 3 H), 1.17 (s, 3 H), 1.29 (br,s, 10 H). 1.64-1.70 (br,s, 6 H), 1.82-2.13 (m, 4 H), 3.8-4.1 (m, 1 H).

MS (m/e) : 290, 292 (M^+).

Anal. Calcd for $C_{14}H_{27}BrO$: C, 57.72; H, 9.36.

Found: C, 58.04; H, 9.45.

Bromoether 2h:[91] Alcohol **1h** (1.54 g, 10 mmol) and NBS (1.96 g, 11 mmol) in CCl_4 under conditions described previously yielded the bromoether **2h**[91] (1.84 g, 79%) as an oil after chromatographic purification.

IR (neat) : 2920, 2860, 1440, 1150, 890 cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ 1.56 (br,s, 10 H), 1.74-1.80 (m, 4 H), 3.20-3.32 (dd, 1 H). 3.42-3.46 (dd, 1 H), 4.2 (m, 1 H).

MS (m/e) : 232, 234 (M^+).

Anal. Calcd for $C_{10}H_{17}BrO$: C, 51.51; H, 7.36.

Found: C, 51.72; H, 7.42.

Bromoether 2i:[91] Alcohol **1i** (1.4 g, 10 mmol), NBS (1.96 g, 11 mmol) in CCl_4 as earlier described afforded bromoether **2i**[91] (1.62 g, 74%) as an oil.

IR (neat) : 2980, 2860, 1445, 1130, 1020, 895 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.6 (br,s, 8 H), 1.72-1.81 (m, 4 H), 3.19-3.32 (dd, 1 H), 3.43-3.47 (dd, 1 H), 4.22 (m, 1 H).

MS (m/e) : 218, 220 (M^+).

Anal. Calcd for $C_9H_{15}BrO$: C, 49.32; H, 6.91.

Found: C, 49.63; H, 6.98.

Bromoether 2j:[78c,91] A solution of the alcohol **1j** (1.4 g, 10 m mol), NBS (1.96 g, 11 mmol) in CCl_4 as earlier gave bromoether **2j**[78c,91] (1.49 g,68%).

IR (neat) : 2920, 2880, 1440, 1350, 1140, 990, 650 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.26 (br,s, 8 H), 1.76-2.23 (m, 3 H), 3.29-3.53 (dd, 2 H), 4.2-4.41 (m, 2 H).

MS (m/e) : 218, 220 (M^+).

Anal. Calcd for $C_9H_{15}BrO$: C, 49.32; H, 6.91.

Found: C, 49.58; H, 6.97.

Bromoether 2k: Alcohol **1k** (0.5 g, 2 mmol), NBS (0.392 g, 2.2 mmol) in CCl_4 under the same conditions as described earlier gave the bromoether **2k** (0.45 g, 68%) as an oil after chromatographic purification.

IR (neat) : 2920, 2840, 2210, 1450, 1370, 1170, 1030 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 0.88 (t, 3 H), 1.26 (br,s, 12 H), 1.40 (s, 3

H), 1.41 (s, 3 H), 1.45-1.81 (m, 4 H), 2.17-2.2 (m, 2 H), 3.92-4.18 (m, 1 H), 4.32-4.48 (m, 1 H).

MS (m/e) : 327, 329 (M^+-1).

Anal. Calcd for $C_{17}H_{29}BrO$: C, 61.99; H, 8.89.

Found: C, 62.23; H, 8.97.

General Procedure for the preparation of enol ethers 3[79]

Enol ether 3a[79]: Potassium metal (0.117 g, 3 mg atom) in tert-butanol (5 mL) was refluxed until all the potassium metal dissolved (~1.5 h). After cooling the solution to 60 °C, bromoether **2a** (0.699 g, 3 mmol) in THF (2 mL) was quickly added. A cream colored precipitate (KBr) started forming immediately. The reaction mixture was stirred at 50-60 °C for 1 h. Then tert-butanol was removed under reduced pressure, petroleum ether (40-60 °C) (20 mL) was added and it was filtered through a pad of Celite. Evaporation of solvent under reduced pressure yielded the enol ether **3a**[79] (0.437 g, 96%). The enol ether was used as such in the next step without purification.

IR (neat) : 3080, 1705, 1640, 1450, 1370, 1140, 1020, 920 cm^{-1}

^1H NMR (CCl_4) : δ 1.23 (s, 3 H), 1.44 (s, 3 H), 1.53 (s, 3 H) 1.6-1.9 (m, 2 H), 2.23-2.47 (m, 2 H), 4.83-5.18 (m, 2 H), 5.6-5.9 (m, 1 H).

Enol ether 3b

IR (neat) : 3070, 1708, 1635, 1455, 1375, 1150, 1000, 920 cm^{-}

^1H NMR (CCl_4) : δ 1.20 (s, 3 H), 1.43 (s, 3 H), 1.6 (s, 3 H), 1.62-1.94 (m, 2 H), 2.1-2.43 (m, 4 H), 4.71-5.06 (m,

H), 5.32-5.98 (m, 1 H).

Enol ether 3c

IR (neat) : 3300, 2100, 1705, 1460, 1440, 1370, 1130, 1060, 980 cm^{-1}.

^1H NMR (CCl_4) : δ 1.52 (s, 3 H), 1.58 (s, 3 H), 2.1 - 2.3 (m, 2 H) 2.23 (s, 1 H).

Enol ether 3d

IR (neat) : 1705, 1455, 1370, 1130, 1015 cm^{-1}.

^1H NMR (CCl_4) : δ 1.6, 1.63 (2 s, 6 H), 2.16-2.23 (m, 2 H).

Enol ether 3e

IR (neat) : 3080, 3060, 3020, 1705, 1600, 1495, 1455, 1375, 1130, 1020, 750, 700 cm^{-1}.

^1H NMR (CCl_4) : δ 1.68 (s, 6 H), 2.1-2.32 (m, 4 H), 2.92 (s, 2 H).

Enol ether 3f

IR (neat) : 3080, 3060, 3020, 1710, 1600, 1490, 1445, 1370, 1130, 970, 900, 765, 700 cm^{-1}.

^1H NMR (CCl_4) : δ 1.46, 1.53 (2 s, 6 H), 2.0-2.23 (m, 2 H).

Enol ether 3g

IR (neat) : 2960, 2940, 2870, 1705, 1450, 1370, 1140, 860 cm^{-1}

^1H NMR (CCl_4) : δ 1.58, 1.62 (2 s, 6 H), 2.1-2.22 (m, 2 H).

Enol ether 3h

IR (neat) : 3090, 2960, 2860, 1685, 1450, 1160, 1070, 960 cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ 2.56-2.72 (t, 2 H), 3.75 (s, 1 H), 4.19 (s, 1 H).

Enol ether 3i

IR (neat) : 3080, 2960, 2860, 1680, 1450, 1160, 1070, 950 cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ 2.52-2.73 (t, 2 H), 3.81 (s, 1 H), 4.21 (s, 1 H

Enol ether 3j

IR (neat) : 3080, 2960, 2860, 1680, 1450, 1160, 1060, 960 cm^{-1}

^{1}H NMR ($CDCl_3$) : δ 2.1-2.32 (m, 2 H), 4.13-4.38 (m, 1 H), 3.91 (s, 1 H), 4.16 (s, 1 H).

Enol ether 3k

IR (neat) : 2920, 2830, 2210, 1705, 1450, 1370, 1140, 1060 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 1.38 (s, 3 H), 1.40 (s, 3 H), 2.17-2.32 (m, 4 H), 4.32-4.48 (m, 1 H).

General procedure for the oxidative cleavage of enol ethers to lactones with PCC

Oxidation of 3a with PCC:

To a stirred mixture of pyridinium chlorochromate (PCC) (1.72 g, 8 mmol) and Celite (1.7 g) in dry dichloromethane (10 mL) was added a solution of crude enol ether **3a** (0.304 g, 2 mmol) in dry dichloromethane (2 mL) at room temperature (28 ^oC). The reaction mixture was stirred for 2 h and then was diluted with ether (50 mL). After filtering through a pad of Celite and silica gel, the filtrate was evaporated and the

residue was purified by flash chromatography on silica gel (elution with 1:4, ether-pet ether) to afford lactone **4a**[92] (0.227 g, 90%) as a colorless oil.

IR (neat) : 3090, 1780, 1650 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.43 (s, 3 H), 1.89-2.20 (m, 2 H), 2.31-2.56 (m, 2 H), 5.03-5.33 (m, 2 H), 5.73-6.04 (m, 1 H).

MS (m/e) : 126 (M^+).

Lactone 4b[93]

A mixture of enol ether **3b** (0.332 g, 2 mmol), PCC (1.72 g, 8 mmol) and Celite (1.7 g) in CH_2Cl_2 (10 mL) was treated as earlier for 2 h to give lactone **4b**[93] (0.249 g, 89%).

IR (neat) : 3060, 1770, 1640 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.42 (s, 3 H), 1.8-2.8 (m, 6 H), 4.9-5.31 (m, 2 H), 5.52-6.2 (m, 1 H).

MS (m/e) : 140 (M^+).

Lactone 4c

Enol ether **3c** (0.3 g, 2 mmol) was treated with PCC (1.72 g, 8 mmol) and Celite (1.7 g) in CH_2Cl_2 (10 mL) for 2.5 h to yield lactone **4c** (0.174 g, 70%).

IR (neat) : 3300, 2100, 1780 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.72 (s, 3 H), 2.12-2.25 (m, 1 H), 2.48-2.68 (m, 3 H), 2.6 (s, 1 H).

MS (m/e) : 124 (M^+).

Anal. Calcd for $C_7H_8O_2$: C, 67.72; H, 6.51.

Found: C, 67.91; H, 6.62.

Lactone 4d[88b,92a,94]

Enol ether **3d** (0.308 g, 2 mmol) was treated with PCC (1.72 g, 8 mmol) and Celite (1.7 g) in CH_2Cl_2 (10 mL) for 2 h as above to yield lactone **4d**[88b,92a,94] (0.218 g, 85%).

IR (neat) : 1770 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 0.96-1.1 (t, 3 H), 1.38 (s, 3 H), 1.53-1.67 (m, 2 H), 1.76-1.97 (m, 2 H), 2.29-2.4 (m, 2 H).

MS (m/e) : 128 (M^+).

Lactone 4e[94]

Mixture of enol ether **3e** (0.432 g, 2 mmol), PCC (1.72 g, 8 mmol) and Celite (1.7 g) in CH_2Cl_2 (10 mL) was treated as earlier for 2.5 h to afford the lactone **4e**[94] (0.312 g, 82%).

IR (neat) : 3080, 3060, 3020, 1770, 1600 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.44 (s, 3 H), 1.91-2.15 (m, 2 H), 2.16-2.27 (m, 1 H), 2.35-2.50 (m, 1 H), 2.94 (d, 2 H, J = 3.75 Hz), 7.21-7.35 (m, 5 H).

MS (m/e) : 190 (M^+).

Lactone 4f[61,62,95]

Enol ether **3f** (0.404 g, 2 mmol) was treated with PCC (1.7 g, 8 mmol) and Celite (1.7 g) in CH_2Cl_2 (10 mL) for 1.5 h as described earlier to give lactone **4f**[61,62,95] (0.264 g, 75%).

IR (neat) : 3080, 3060, 1775, 1600 cm^{-1}.

^1H NMR ($CDCl_3$): δ 1.72 (s, 3 H), 2.35-2.69 (m, 4 H), 7.3 (s, 5 H).

MS (m/e) : 176 (M^+).

Lactone 4g[88b,96c]

Enol ether **3g** (0.420 g, 2 mmol) was treated with PCC (1.72 g, 8 mmol) and Celite (1.7 g) in CH_2Cl_2 (10 mL) as described earlier to give the lactone **4g**[88b,96c] (0.290 g, 79%).

IR (neat) : 1780 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 0.90 (t, 3 H), 1.35 (s, 3 H), 1.2-1.6 (br,s, 10 H), 1.71-2.13 (m, 2 H), 2.47-2.60 (m, 2 H).

MS (m/e) : 184 (M^+).

Lactone 4h[62,96,97]

A mixture of enol ether **3h** (0.304 g, 2 mmol), PCC (1.72 g, 8 mmol) and Celite(1.7 g) in CH_2Cl_2 (10 mL) was stirred for 1.5 h to give the lactone **4h**[62,96,97] (0.203 g, 66%) after flash chromatography.

IR (neat) : 1780 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.2-1.9 (m, 10 H), 2.04 (t, 2 H, J = 8 Hz), 2.62 (t, 2 H, J = 8 Hz).

MS (m/e) : 154 (M^+).

Lactone 4i[62,96b,97]

Enol ether **3i** (0.276 g, 2 mmol) was treated with PCC (1.72 g, 8 mmol) and Celite (1.7 g) in CH_2Cl_2 (10 mL) for 1 h as described earlier to afford lactone **4i**[62,96b,97] (0.157 g, 56%).

IR (neat) : 1770 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.5-2.0 (m, 8 H), 2.12-2.53 (t, 2 H), 2.51-2.75 (t, 2 H).

MS (m/e) : 140 (M^+).

Lactone 4j[61,98]

Enol ether **3j** (0.276 g, 2 mmol), PCC (1.72 g, 8 mmol) and Celite (1.7 g) in CH_2Cl_2 (10 mL) were allowed to react for 1.5 h

as described earlier to give the lactone **4j**[61,98] (0.143 g, 51%).

IR (neat) : 1780 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.1-2.12 (m, 8 H), 2.13-2.7 (m, 3 H), 3.82-4.06 (m, 1 H).

MS (m/e) : 140 (M^+).

Lactone 4k[66]

Enol ether **3k** (0.248 g, 1 mmol) was treated with PCC (0.86 g, 4 mmol) and Celite (0.86 g) in CH_2Cl_2 (7 mL) for 1.5 h as described earlier to afford the lactone **4k**[66] (0.115 g, 52%) after chromatographic purification.

IR (neat) : 2200, 1780 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 0.87 (t, 3 H), 1.26 (m, 12 H), 2.21-2.63 (m, 6 H), 5.06-5.35 (m, 1 H).

MS (m/e) : 222 (M^+).

(±)-(Z)-5-Tetradecen-4-olide 31[66]

Palladium on barium sulfate (50 mg, 5%) and quinoline (1 drop) were added to a solution of (±) **4k** (0.111 g, 0.5 mmol) in 25 mL of ether. The mixture was stirred under hydrogen atmosphere at room temperature for 12 h. The concentrated filtrate was subjected to column chromatography on silica gel to afford (±)**31**[66] (0.106 g, 95%) as a colorless oil.

IR (neat) : 3020, 2940, 2860, 1785, 1660, 1460, 1220, 1180, 1015, 980, 720 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 0.89 (t, 3 H), 1.0-1.48 (bs, 12 H), 1.5-2.5 (m, 6 H), 5.08 (m, 1 H), 5.20-5.66 (m, 2 H).

MS (m/e) : 224 (M^+)

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CHAPTER IB

STUDIES ON THE MECHANISM OF THE SUBSTITUENT DIRECTED OXIDATIVE CYCLIZATION REACTION

IB.1 : INTRODUCTION

Enzymatic processes are highly regio- and stereo-selective and yield pure product enantiomers from non chiral precursors, which are to be admired and imitated by synthetic chemists.[1] Synthetic methods are needed which can meet the same high standards of chemical yield and purity of the desired product that we see in biochemical reactions. Substituent directed transformation elicits high degree of stereo-and regio-selectivity, which is a basic requisite in the chemical architecture of natural product synthesis.[2] The intramolecular[3] nature of this transformation imposes geometric constraints on the transition state from which the high specificity arises.

The potential of the substituent (hydroxyl) directed reactions[4] has been well demonstrated by Sharpless[5] in the epoxidation of olefins. When the substrate olefin is an allylic alcohol, the transition metal forms a complex with hydroxyl group and directs the regio- and stereo-chemistry of the epoxidation reaction. Similar kind of regio- and stereo-selectivity has been observed in Simmons-Smith cyclopropanation[6] of allylic alcohols. Recently, Stork[7] reported a high degree of stereochemical control by hydroxyl group in the homogeneous catalytic hydrogenation of olefins with iridium complex and

similar observations have been reported by Schultz,[8a] Brown[8b] and Evans.[8c]

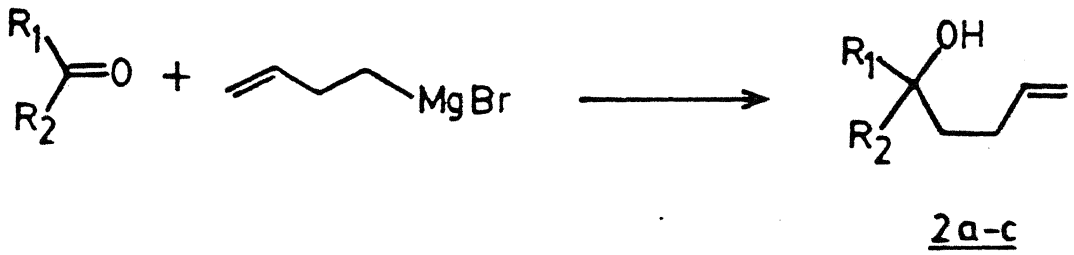
Breslow achieved a template-directed epoxidation of steroidal double bond[9] and 'Radical-Relay' chlorination[10] of steroids under template control.

Herz[11] observed a hydroxyl directed oxidation of allylic alcohols to α,β-epoxy aldehydes with high degree of product selectivity.

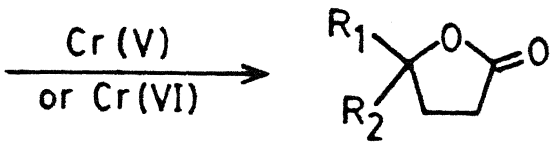
Earlier work from our laboratory has shown that substituent (hydroxyl) directed oxidative cyclization of ω-hydroxy olefins **2** to lactones **4**[12] with oxo-chromium(V) reagent, $BiPyH_2CrOCl_5$[13] or oxo-chromium(VI) reagent, pyridinium chlorochromate (PCC).[14] The overall transformation involves a net loss of one or more carbon atoms (**Scheme IB.1.1**). Oxidative cyclization in a substrate that contains both a site for oxidative attack (such as an alkene) and an interactive nucleophile or ligand substituent (such as a hydroxyl) constitutes a useful selective synthetic method and provides a discriminating test for different oxidants and oxidation pathways.[15] Schlecht and Kim[16] observed a similar type of oxidative cyclization using modified Fieser's reagent ($CrO_3/Ac_2O/AcOH$).

Chromium(V) reagents are known[17] to cleave carbon-carbon double bond and hence it is easy to visualize the formation of hemiacetals **3a-c** which on further oxidation can lead to γ-lactones **4a-c** (**Scheme IB.1.2**). On the other hand hexavalent chromium reagents like pyridinium chlorochromate (PCC)[14] or

Scheme-IB-1.1



2a-c



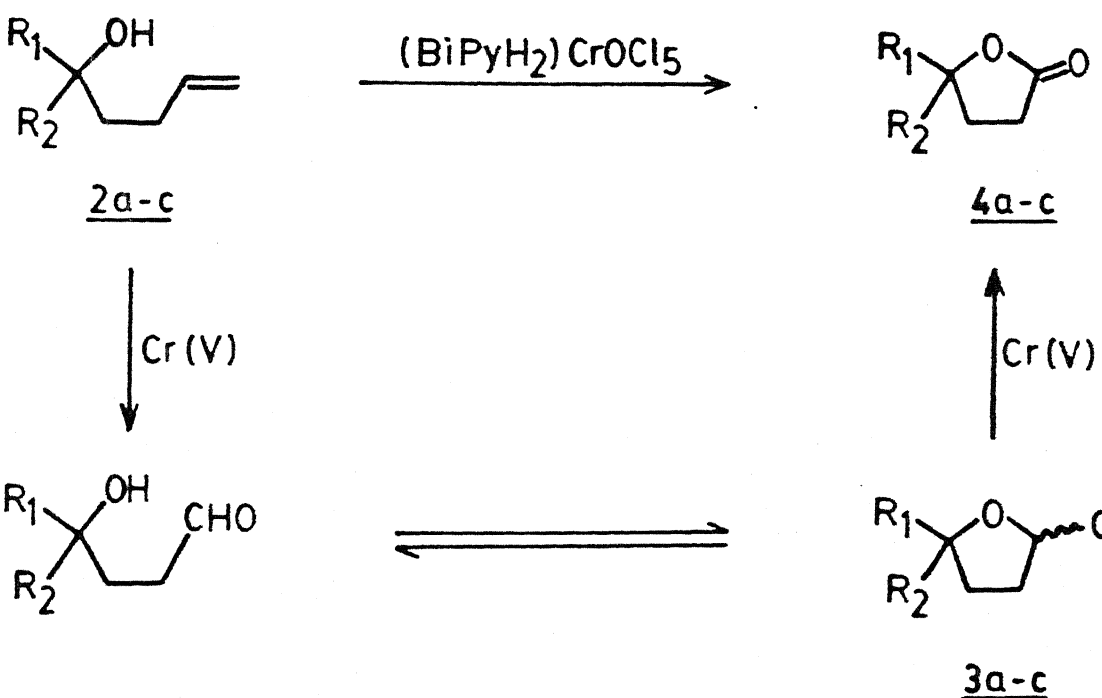
4a-c

a : $R_1 = R_2 = -CH_3$

b : $R_1, R_2 = -(CH_2)_4-$

c : $R_1, R_2 = -(CH_2)_5-$

Scheme-IB-1.2



a : $R_1 = R_2 = -CH_3$, b : $R_1, R_2 = -(CH_2)_4-$, c : $R_1\ R_2 = -(CH_2)_5-$

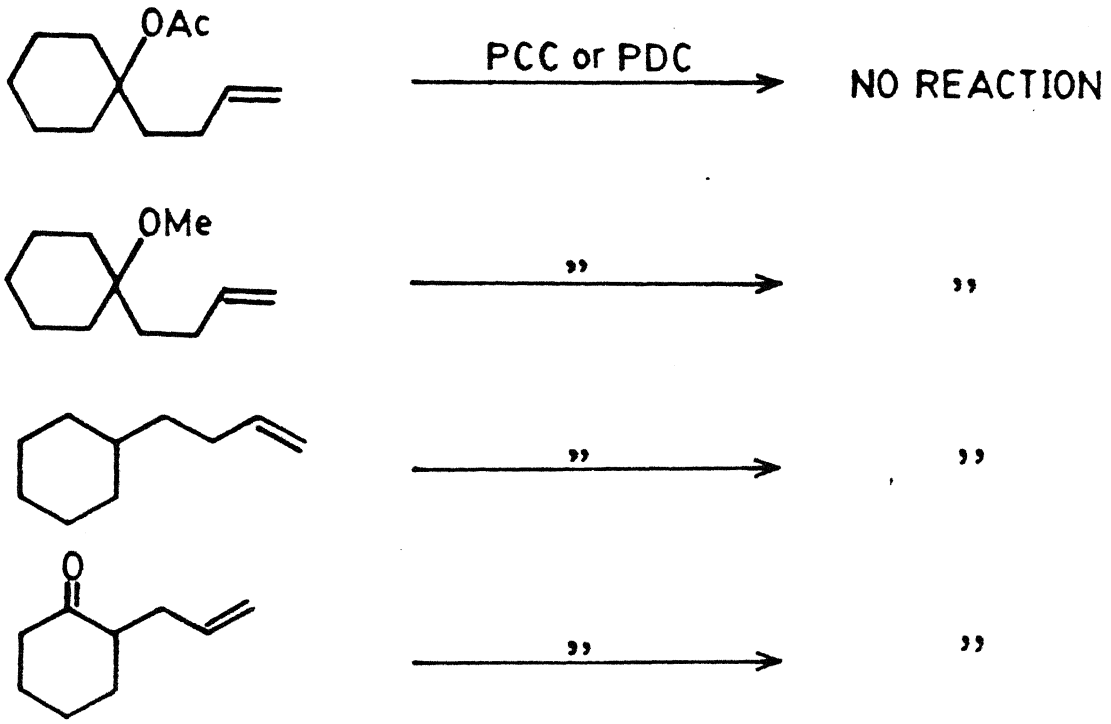
pyridinium dichromate (PDC)[18] which have been shown[19] to be inert to isolated double bonds also effect this oxidative cyclization. Apart from this process being a good synthetic methodology, it is intriguing and provocative from the mechanistic point of view.

This transformation is clearly substituent (hydroxyl) directed oxidation,[20] since the acetate of the alcohol **2a**, or with other functional group in lieu of hydroxyl group, under the reaction conditions (PCC, CH_2Cl_2, reflux, 48 h) remained unchanged. (**Scheme IB.1.3**)).

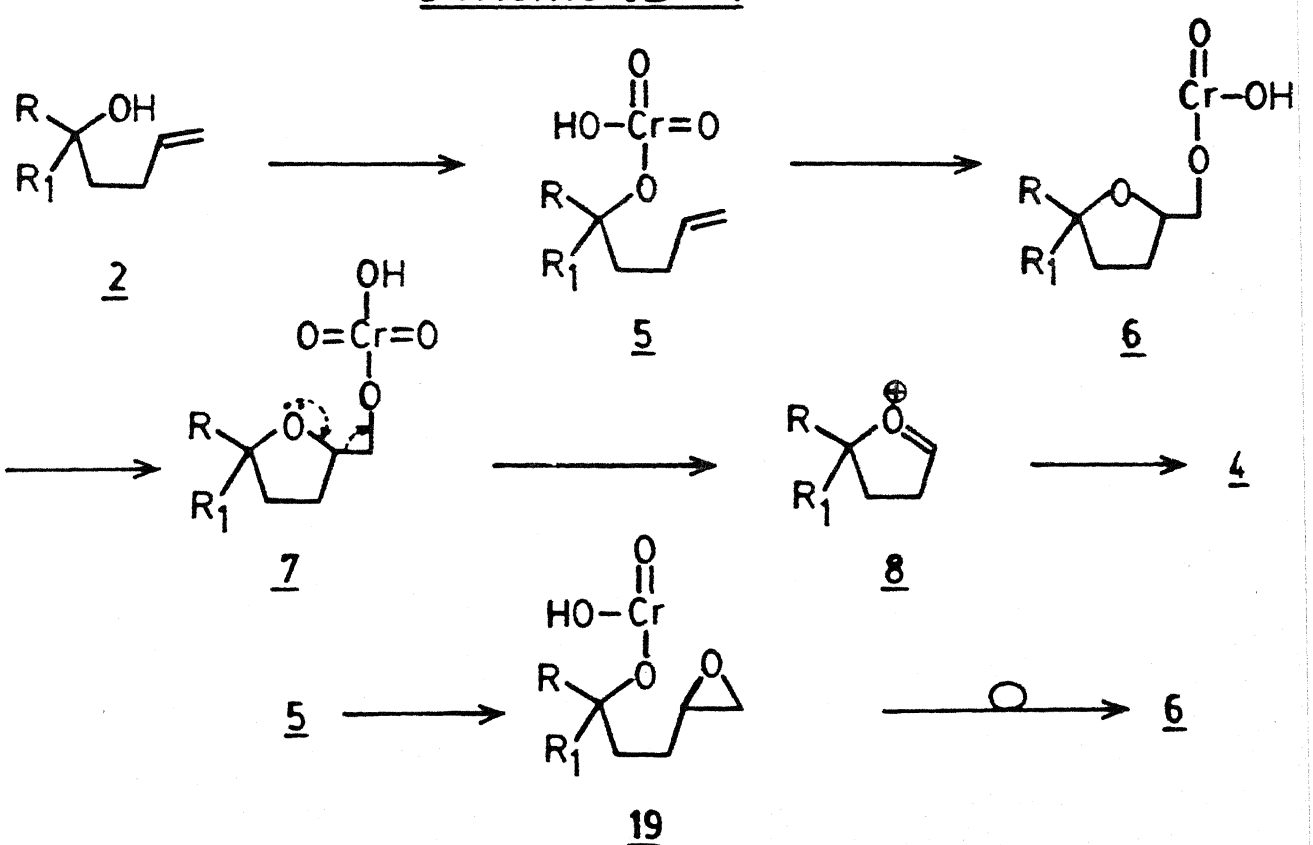
The substituent hydroxyl group can direct the oxidative cyclization in two possible modes: The **type I** involving initial activation of the hydroxyl ligand substituent by the oxidant followed by a secondary oxidative attack on the alkene and the **type II** involving initial oxidative activation of the alkene to form an intermediate, which is attacked in a second step by the nucleophilic hydroxyl substituent.

In the **type I** process involving a prior binding of the oxidant, the relative geometry of approach of the bound oxidant to the substrate is constrained and the structure of the transition state for oxidative attack would be better defined than in an intermolecular oxidative attack.[5b] This restricted approach of the complexed oxidant to the site of attack will lead to a much higher degree of product selectivity. Processes following this pathway include Sharpless epoxidation[5] of the allylic alcohols, Stork's catalytic hydrogenation[7] of hydroxy

Scheme-IB-1.3



Scheme-IB-1.4



olefins under homogeneous conditions, Breslow's template directed halogenation[10] and epoxidation[9] of steroids and Baldwin's penicillin bio-synthesis that involves attack by a sulfur-bound iron(IV) oxide upon an alkyl (or alkenyl) side chain substrate.[21] In the **type II** process, intermediate formed by initial intermolecular attack of the oxidant on the alkene can be efficiently trapped through intramolecular attack by the hydroxyl group. Processes following this pathway include the "elemento etherification" reactions effected, for example, by selenenyl halides[22] and lead(IV)[23] and thallium(III)[24] reagents. In both types of mechanism, the special character of intramolecular reactivity due to the influence of an interactive substituent translates into higher product selectivity.[5-10]

Schlecht and Kim[16] have proposed a mechanism for the oxidative cyclization of ω-hydroxy olefins to lactones with modified Fieser's reagent, invoking oxonium ion **8** as the key intermediate (**Scheme IB.1.4**). A syn-electrophilic attack of chromate ester 5 on olefin would lead to the chromium(IV) ester **6**. Reoxidation of the metal followed by oxidative fragmentation would give oxonium ion **8**, which on further exposure to excess oxidant would yield the lactone product **4**.

An alternative pathway for the transformation of **5 --> 6** proceeds through epoxidation and solvolytic opening, as shown in **Scheme IB.1.4.** This **scheme IB.1.4** however, does not offer any explanation for the carbon-carbon bond cleavage as depicted.

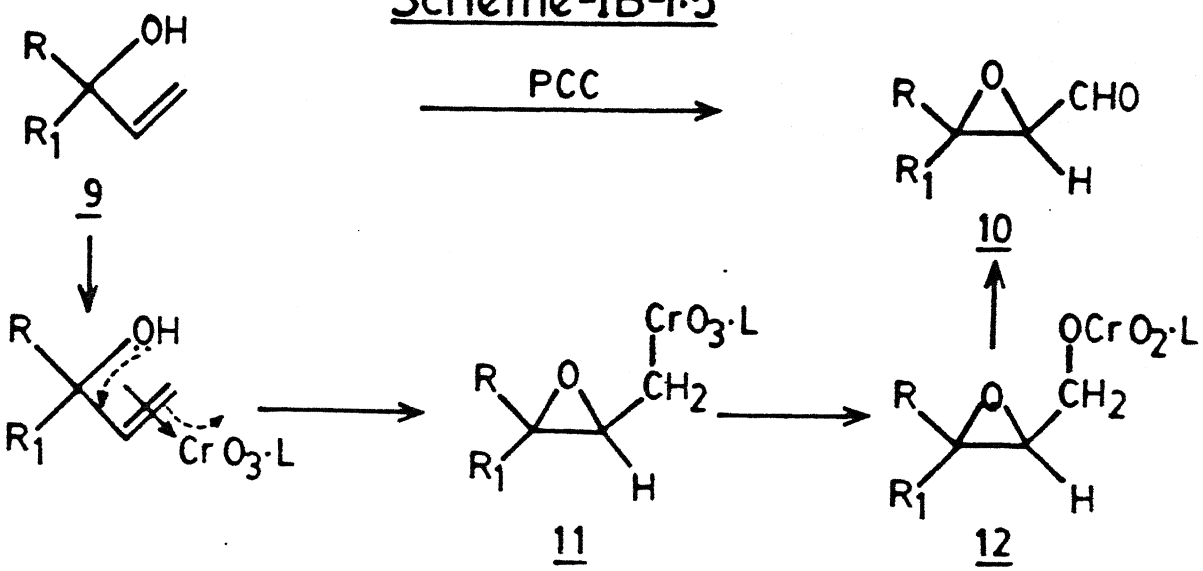
A related reaction of allylic alcohol with pyridinium chlorochromate is worth mentioning from the mechanistic view

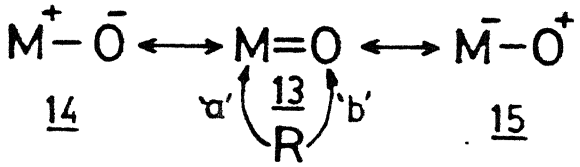
point. Herz and Sundararaman[11] have shown that the oxidation of allylic alcohols like **9** on treatment with PCC yield the α,β-epoxy carbonyl compounds **10** as the major product (**Scheme IB.1.5**). The suggested mechanism for the oxidative rearrangement involves initial formation of a π-complex of the oxidant with olefin, followed by nucleophilic attack by hydroxyl group to give intermediate **11** with a C-Cr sigma bond which can further rearrange to chromate ester **12**, the precursor of epoxy aldehyde **10**.

Sharpless[25] has proposed a general mechanistic pathway for the oxidation of olefins with high valent oxo-transition metal species which is supported by a recent ab initio theoretical calculations of Rappe and Goddard.[26] Certain oxo-metal species such as Cr(VI) oxide, Mo(VI) oxide, Mn(VII) oxide and Ru(VIII) oxide have been found to be useful in organic synthesis because of their ability to selectively transfer oxygen atoms to olefins[27,28] and other organic substrates.[28]

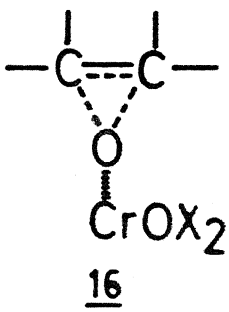
In most of the oxygen transfer reactions, the mechanism postulated involved direct attack of the organic reductant (R, path b) on the oxygen end of the oxo-moiety[15] **13** implying polarization of the oxo group as indicated in resonance form **15**. However, the oxo groups in such oxidants are clearly better represented by the dipolar resonance structure **14** (Eqn. 1) and Sharpless[25] provided evidence for the fact that these oxidations are more likely initiated by attack of the organic reductant at the metal center (path a) leading by indirect routes, through organometallic intermediate, to the observed products.

Scheme-IB-1.5



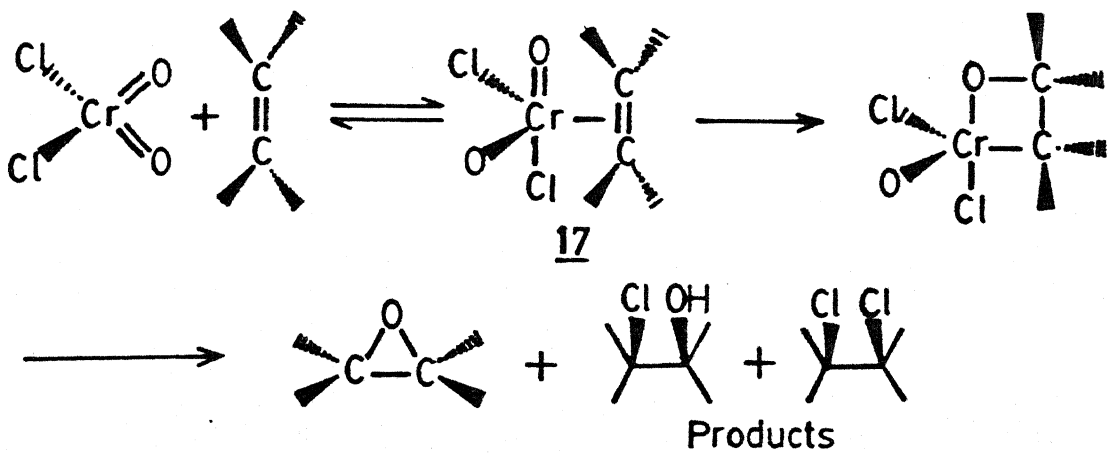


---------- eq. 1



---------- eq. 2

Scheme-IB-1.6



Several mechanisms have been suggested for the epoxidation of alkenes by chromyl complexes.[29] Until recently, a symmetric three-membered cyclic activated complex **16**, had been considered as the transition state[15] (Eqn. 2). This satisfies the mechanistic criteria and accounts as well for the electrophilic character of the chromyl complexes, but it fails to explain the formation of cis-chlorohydrin and cis-vicinal dichloride. However, a novel mechanism based on low-temperature oxidation of olefin with chromyl chloride has been invoked by Sharpless,[25] which is outlined in **Scheme IB.1.6.**

The first step involves the formation of chromyl chloride olefin π-complex **17**, followed by a [2+2] cycloaddition of the alkene to the oxo-chromium bond, giving a chromoxetan **18** which decomposes as shown in **Scheme IB.1.6.** In the case of ligands more basic than an olefin, stable complexes related to **17** are well known (e.g., CrO_3.2Py and OsO_4.Py).

Theoretical investigations,[26] using ab initio generalized valence bond calculations, have shown that the formation of metallo-oxetane **18** is exothermic by 14 Kcal.mol^{-1} whereas a direct addition of olefin to the oxo-ligands in chromyl chloride 16, is endothermic by 56 Kcal.mol^{-1}. Calculated activation energy favours the formation of metallo-oxetane 18 over the formation of three-membered cyclic activated complex **16.** Now the literature abounds with examples of stable, high-valent organometallic derivatives of chromium,[30] niobium,[31] tantalum,[31] tungsten[32] and rhenium.[33]

Thus, taken together with the afore mentioned observations, Sharpless proposal[25] would be the likely process in the oxidation of alkenes with oxo-transition metal species and these modern ideas of Sharpless would be taken into account, in explaining the substituent (hydroxyl) directed oxidative cyclization of γ-hydroxy olefins **2** to lactones **4** with oxo-chromium(VI) reagents.

IB.2 RESULTS AND DISCUSSION :

The uniqueness of this oxo-chromium(VI) mediated, substituent hydroxyl directed oxidative cyclization of γ-hydroxy olefins to lactones as a selective synthetic method prompted us to study the mechanism of this novel reaction. A few plausible mechanistic pathways have been suggested for this transformation and attempts have been made to substantiate the postulated hypothesis. The substituent hydroxyl can direct the oxidative cyclization in two possible modes :

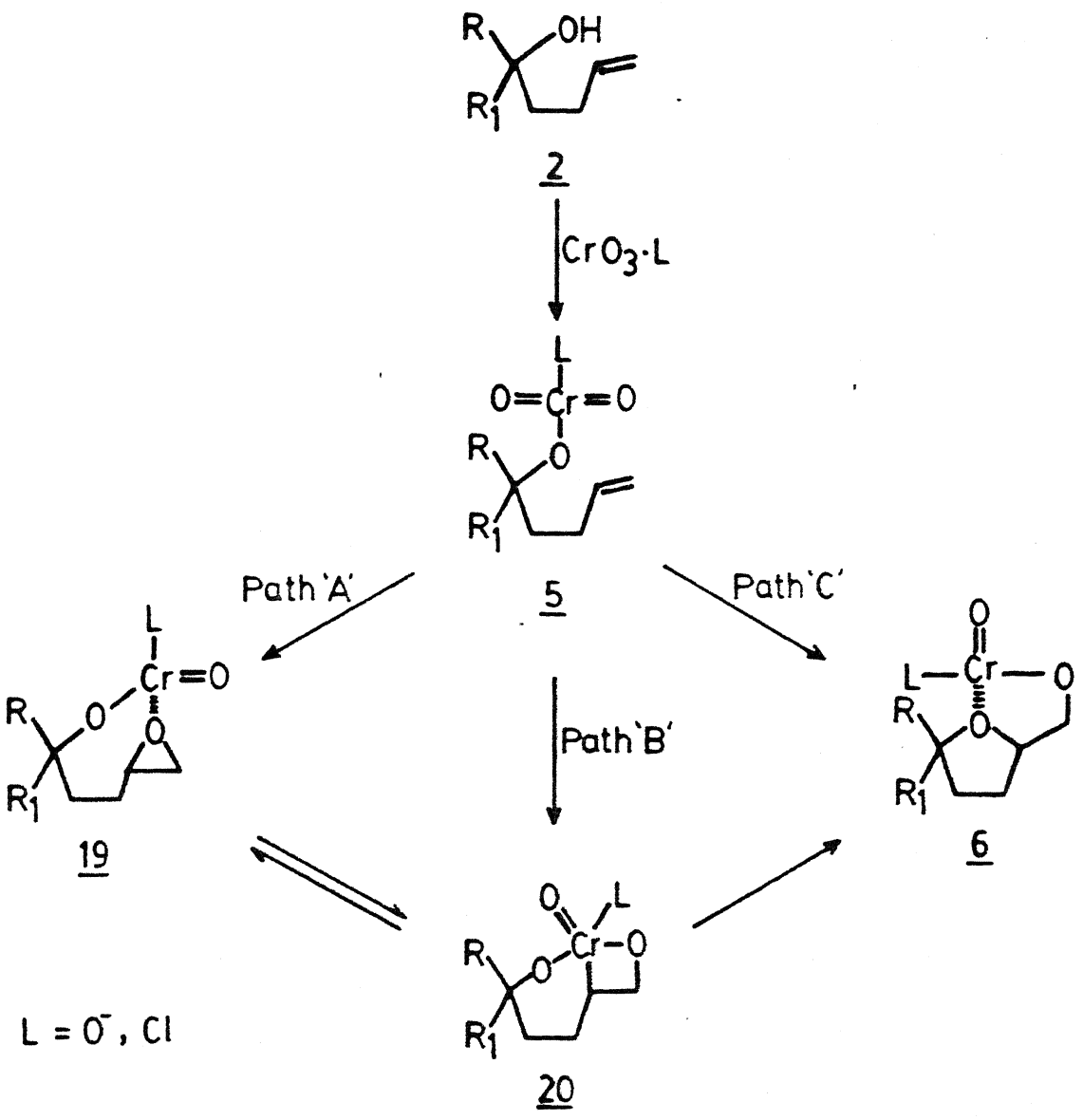
i) One involving the prior formation of a chromate ester which then guides the attack on the olefin, (**Type-I**) as shown in the **Scheme IB.2.1.**

ii) Involving initial activation of the alkene by forming an intermediate π-complex, followed by nucleophilic attack by hydroxyl group (**Type-II**), which is shown in **Scheme IB-2.2.**

Oxo-chromium(VI) reagents are known[34] to form chromium(VI) esters very rapidly with primary, secondary, and tertiary alcohols (**Type-I**). Herz and Sundararaman[11] have invoked both types of attack in explaining the oxidative rearrangement of

Scheme-1B-2·1

TYPE-I



PATH WAY

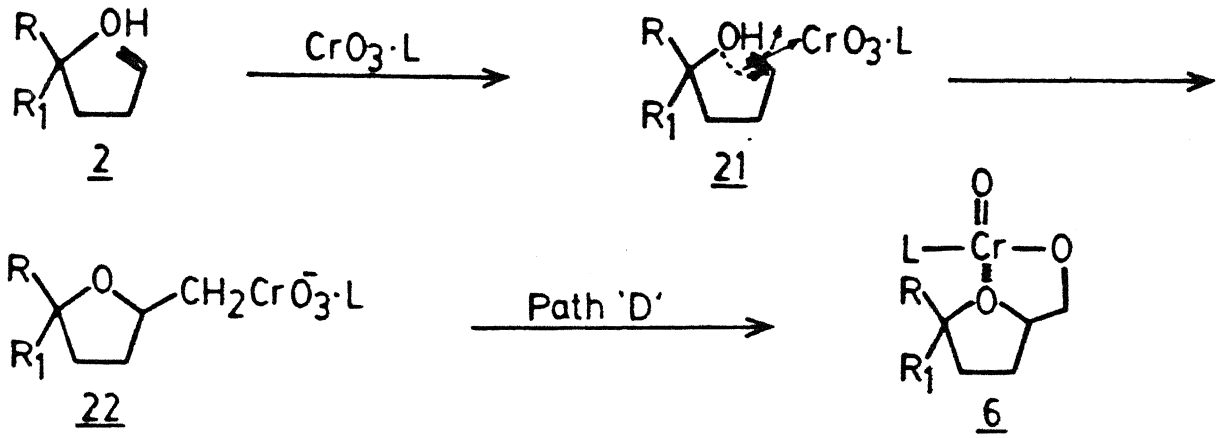
A : Direct epoxidation of the olefin.

B : Formation of metallooxetane by [2+2] Cycloaddition.

C : Criegee [3+2] Cycloaddition, followed by fragmentation.

Scheme-IB-2·2

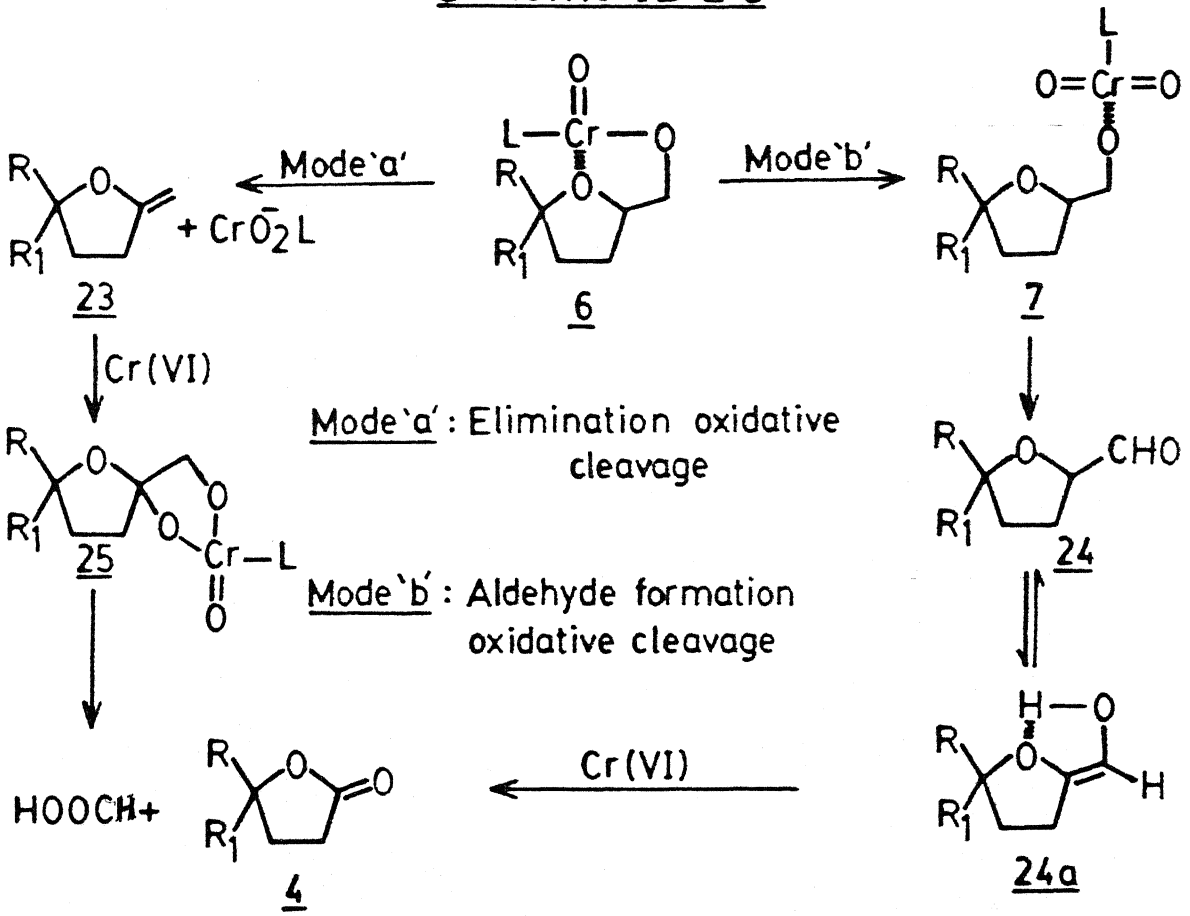
TYPE - II



PATH WAY

D : 1,2-Carbon to oxygen migration of chromium.

Scheme-IB-2·3



allylic alcohols with oxo-chromium(VI) reagents, but prefer the attack of the hydroxyl group on the activated complex of the olefin (**Type-II**) and this proposal is further supported by the recent spectroscopic evidence for the prior formation of a olefin π-complex with OsO_4 using **diadamantylidene** as a non reacting alkene.[35]

In the **type-I** mechanism (**Scheme-IB.2.1**) the preformed chromium(VI) ester **5** can attack the olefin in three different pathways :

i) First pathway involves one or two step oxygen transfer[27,36] from the oxo-metal to alkene, to give an epoxy chromium(IV) ester **19** as the primary product which may rearrange to metallo-oxetane intermediate **20** (**Path A**).

ii) A second formulation involves the formation of an organometallic intermediate metallo-oxetane **20** by [2+2] cycloaddition of oxo-chromium(VI) ester **5** with alkene, which may undergo reductive elimination to the key intermediate chromium(IV) ester **6**, or it may rearrange to epoxy-chromium(IV) ester **19 (Path B).** This pathway would be in line with Sharpless proposals.[25]

iii) A third pathway is the Criegee[37] [3+2] cycloaddition of the oxygen end of the oxo-metal species onto the olefin, followed by fragmentation to give the key intermediate chromium(IV) ester **6**. Theoretical calculations[26] indicate that the Criegee mechanism is energetically unfavourable without the stabilization energy that attends the increase in bond order of a "spectator" metal-oxo group (**Path-C**).

In the **type-II** mechanism (**Scheme-IB-2.2**), oxo-chromium(VI) reagent activates the olefin by forming a π-complex **21**, followed by a nucleophilic attack of the hydroxy group producing intermediate chromium(VI) ester **22** with a chromium sigma bond, which may undergo 1,2-carbon to oxygen migration of the chromium with concomitant reduction of the metal to give the key intermediate chromium(IV) ester **6**. 1,2-Carbon to oxygen migration of metal is known in the transition metal analog of a Vanadyl(V) organometallic derivative.[38]

There are atleast two modes by which the decomposition of the key intermediate chromium(IV) ester **6** to lactone **4** can take place (**Scheme IB.2.3**). It is likely that this chromium(IV) ester **6** can lead to the formation of enol ether **23** (**mode-a**) by elimination. Further reaction of this exocyclic enol ether **23** with excess oxo-chromium(VI) reagent may lead to the γ-lactone **4** by oxidative fragmentation of the intermediate cyclic chromate ester 25. On the otherhand, it is likely that the key intermediate chromium(IV) ester **6** can undergo oxidation with excess reagent to chromium(VI) ester **7** (**mode-b**), followed by decomposition to aldehyde **24**. In presence of excess oxo-chromium(VI) reagent, this aldehyde **24** can undergo oxidative fragmentation through its enol form **24a** to afford the lactone **4** (**Scheme IB.2.3**). Oxidative cleavage of enol of aldehyde with pyridinium dichromate (PDC) is precedented in the literature.[39]

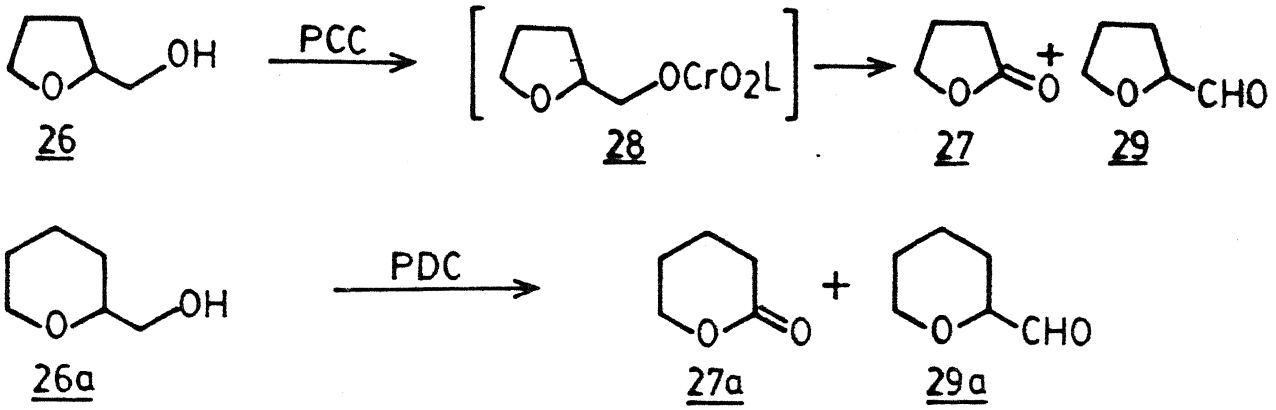
In order to understand this substituent directed oxidative cyclization better and to get further insight into the reaction pathway, it was decided to study this problem from two different

angles. In one approach, model compounds similar to the postulated intermediates can be synthesized and can be subjected to oxidation with oxo-chromium(VI) reagents under the same reaction conditions and course of the reaction can be followed. In the second approach attempts can be made to detect or isolate, if possible, any of the postulated intermediates. Studies related to both these approaches are presented in this chapter.

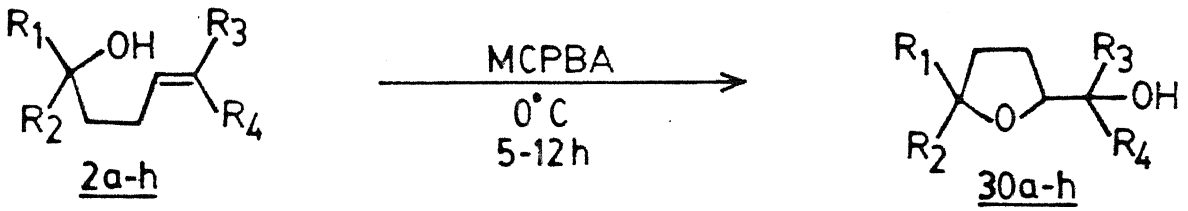
Oxidation Studies with Oxo-Chromium Reagents on Model Compounds Similar to Postulated Intermediates

In both the mechanisms proposed for the oxidative cyclization of γ-hydroxy olefin **2** to lactone **4** (**Scheme IB.2.1** and **IB.2.2**), it is interesting to note that irrespective of the pathways (**a,b,c** or **d**) all of them go through the formation of the chromium(IV) ester **6** as the key intermediate. If this was true, we anticipated that a simple model compound like tetrahydrofurfuryl alcohol **26** should undergo oxidative cleavage with oxo-chromium(VI) reagents by any of the two modes (**a** or **b**, **Scheme-IB.2.3**) suggested. Accordingly when **26** was treated with excess of pyridinium chlorochromate (5 mole equiv.) in dichloromethane under reflux (5 h) or pyridinium dichromate (5 mole equiv.) in dichloromethane (6 h), lactone **27** was obtained as the major product of the reaction (46-51%) and aldehyde **29** (normal product of oxidation) as the minor product (6-8%) (**Scheme IB.2.4**). Treatment of **26** with pyridinium chlorochromate (4 mole equiv.) in dichloromethane at room temperature (28 ^{o}C) for 5 h however, gave a mixture (1:1) of **27** and **29** with a lot of unreacted starting material. This aldehyde **29**, when independently treated with excess of pyridinium chlorochromate

Scheme-IB-2·4



Scheme-IB-2·5



Scheme-IB-2·6

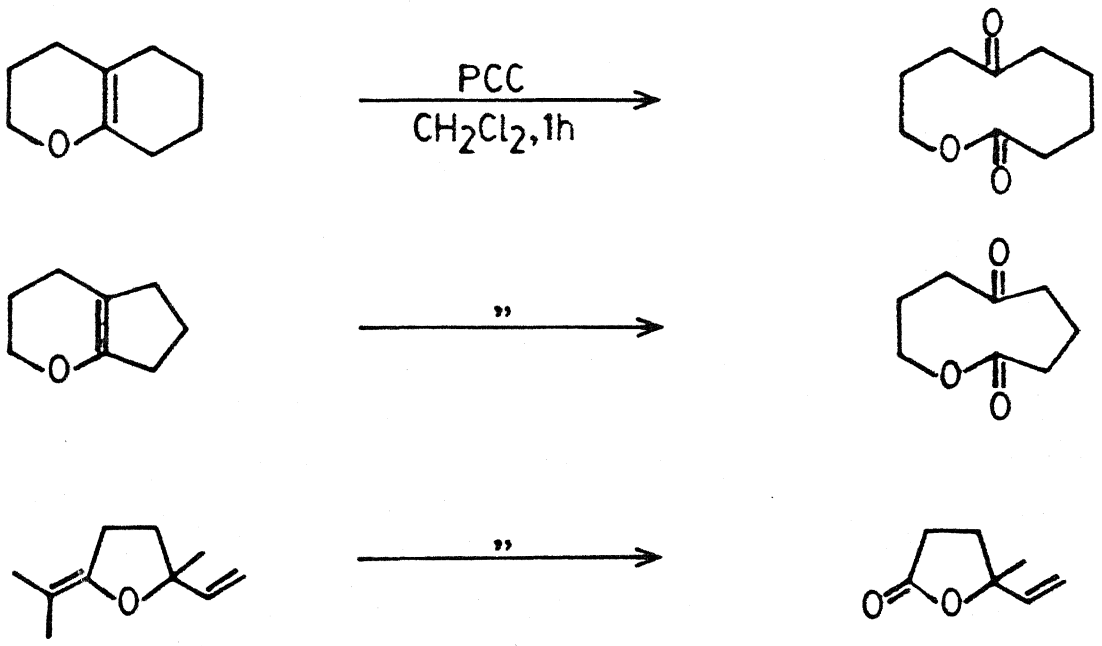


Table-IB-2.1

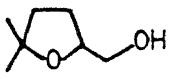
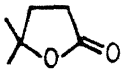
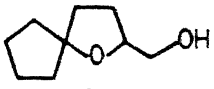
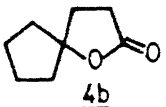
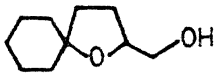
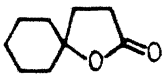
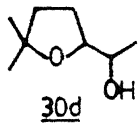
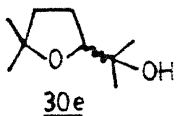
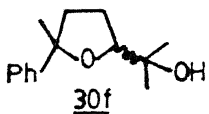
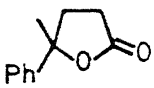
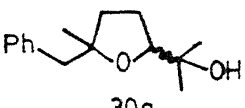
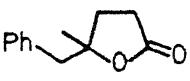
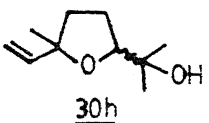
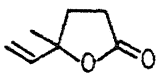
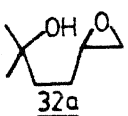
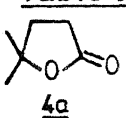
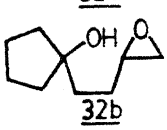
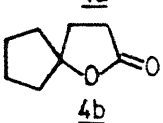
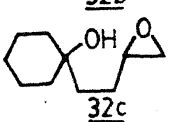
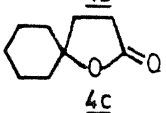
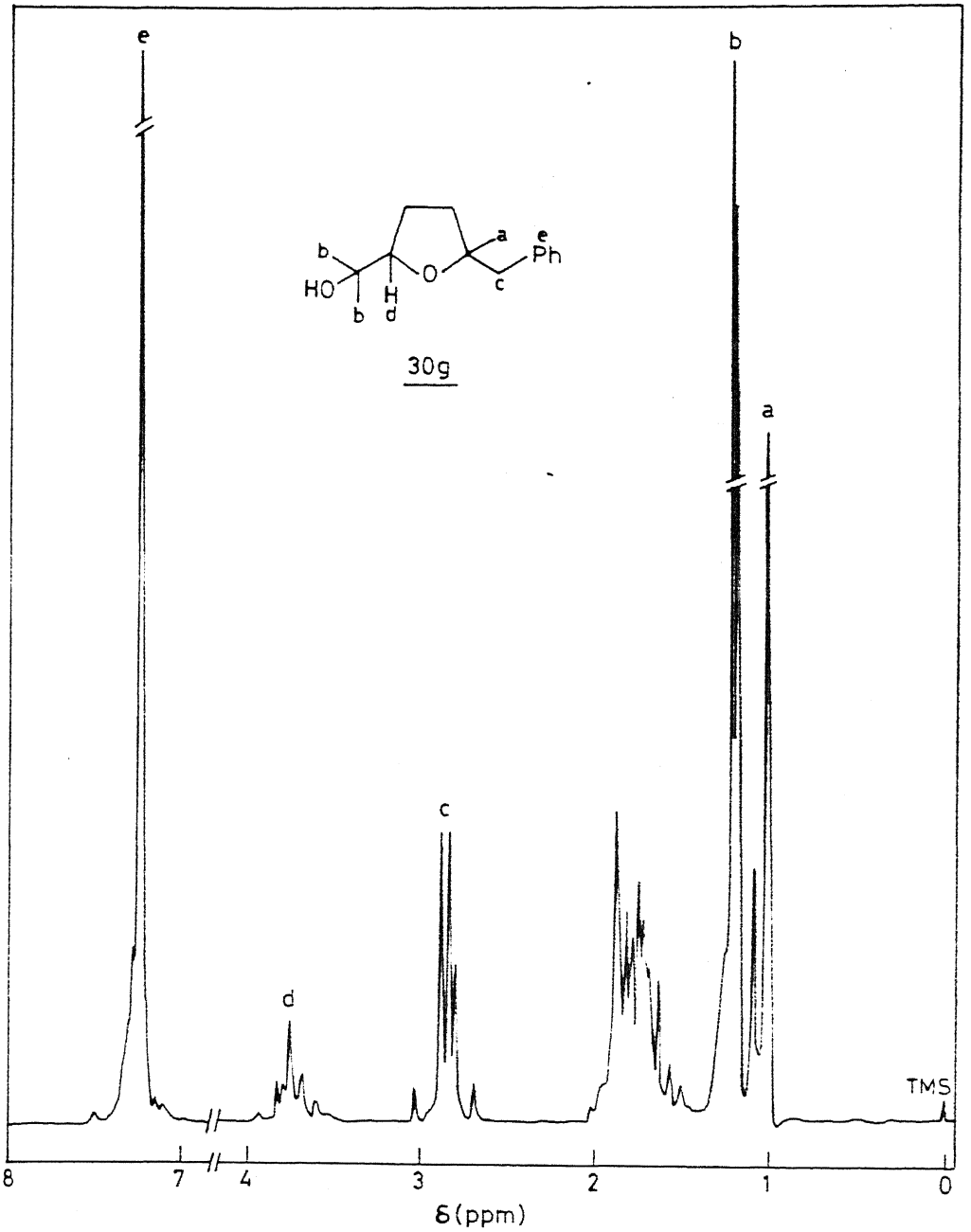
	SUBSTRATE	PRODUCT	YIELD(%)	h
1.	 30a	 4a	53	8
2.	 30b	 4b	58	7
3.	 30c	 4c	54	8
4.	 30d	4a	57	5
5.	 30e	4a	63	4
6.	 30f	 4f	82	3·5
7.	 30g	 4g	95	3
8.	 30h	 4h	73	3

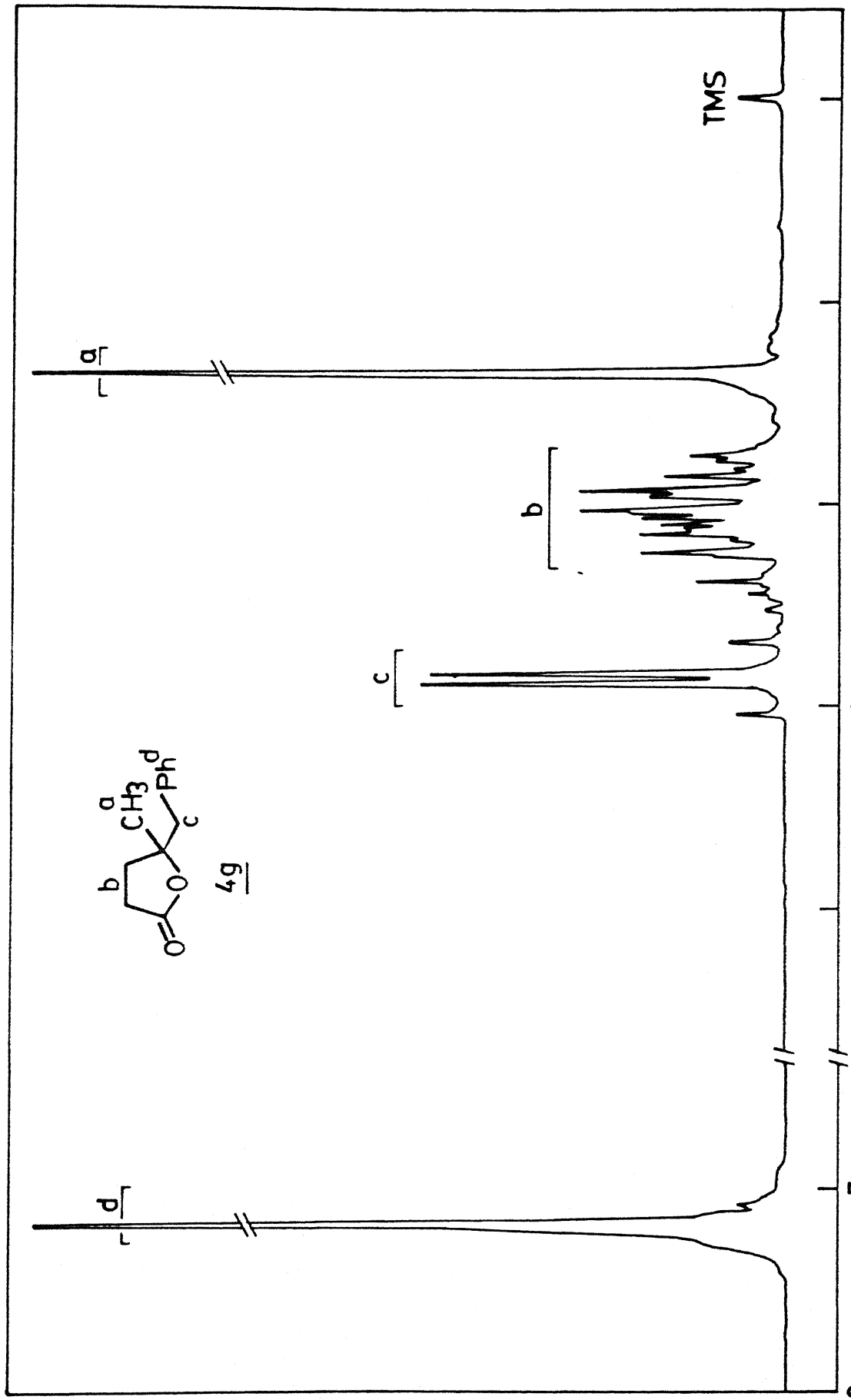
Table-IB-2.2

1.	 32a	 4a	50	8
2.	 32b	 4b	65	6
3.	 32c	 4c	59	8

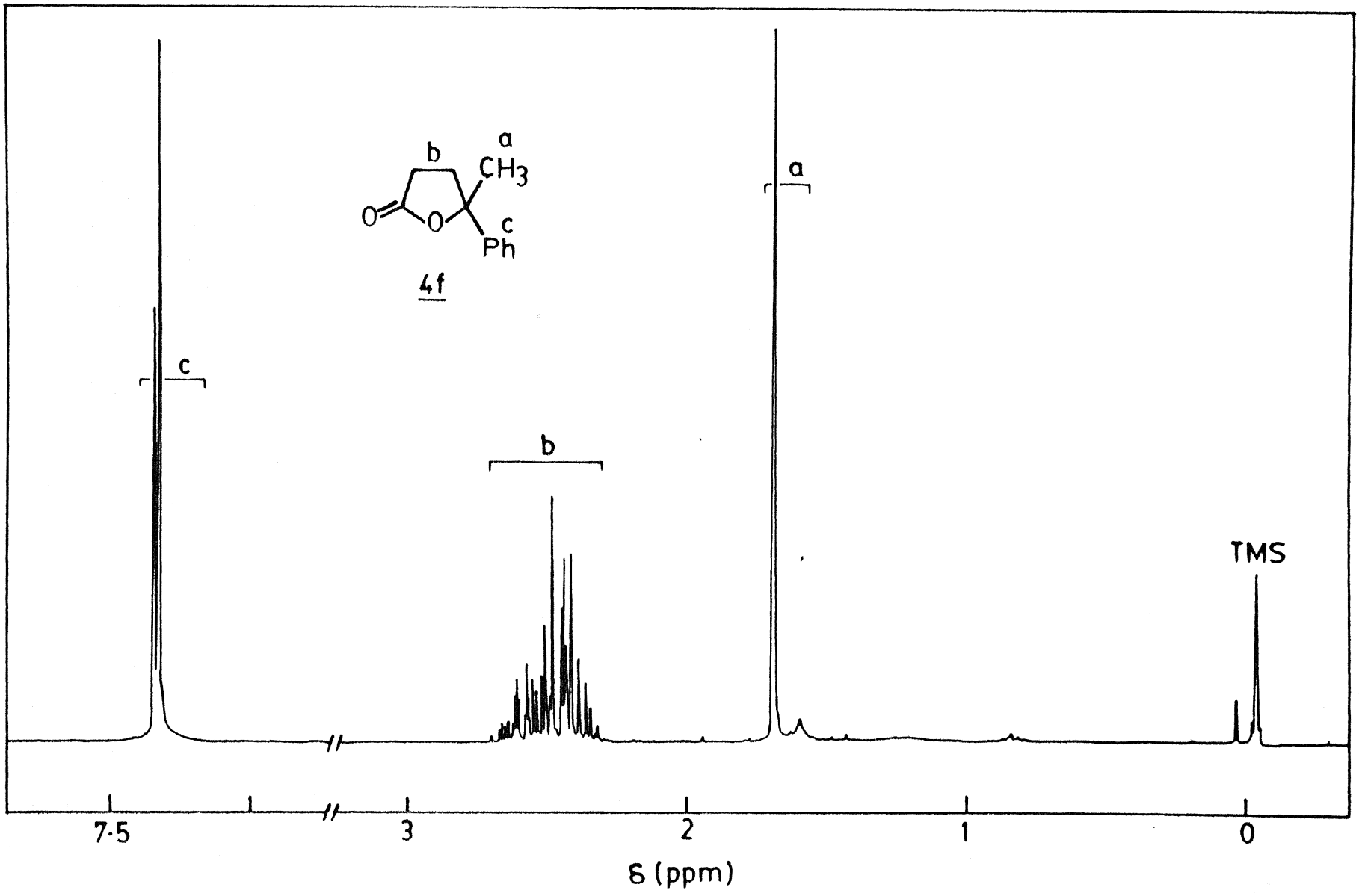


30g

^{1}H NMR Spectrum (90 MHz) of 30g



^{1}H NMR Spectrum (90 MHz) of 4g



^{1}H NMR Spectrum (250 MHz) of 4f

(CH_2Cl_2, 40 °C, 3 h) was converted smoothly to the lactone **27** (55%). Similarly, tetrahydropyran methanol **26a** on treatment with excess pyridinium chlorochromate or pyridinium dichromate (5 mole equiv.) (benzene, 80 °C, 24 h) gave the corresponding δ-lactone **27a** (15%) and the aldehyde **29a** (40%).

It was of interest to find out whether this unusual transformation of tetrahydrofuran methanol **26** to γ-butyrolactone **27** is a general reaction of all tetrahydrofuran methanol derivatives and whether this can be developed as a useful synthetic methodology for the synthesis of a variety of γ-butyrolactones. With this objective a number of tetrahydrofuran methanol derivatives **30a-h** were prepared from the corresponding γ-hydroxy olefins **2a-h** by reaction with m-chloroperbenzoic acid at 0 °C for 7-24 h (**Scheme IB.2.5**)[40,41]. When these tetrahydrofuran methanol derivatives **30a-h** were treated with pyridinium chlorochromate (PCC) (4 mole equiv., molecular sieves 3 A°, CH_2Cl_2, 40 °C, 3-8 h) they underwent a smooth oxidative cleavage to yield the corresponding γ-lactones **4a-h** in high yields (53-95%) (**Table IB.2.1**).

Oxidative transformation of **26** to **27** with other oxidants like O_2[42b], silver carbonate-Celite[42a] and chromic acid[40] have been reported to proceed in low-moderate yield and no mechanistic details are available. The present methodology appears to be very general and the reaction takes place under milder conditions to afford high yield of γ-lactones. This methodology incidentally lends some support (not necessarily conclusive) to the possibility of an intermediate similar to the chromate ester

6 in the oxidative cyclization of γ-hydroxy olefins **2** to γ-lactones **4**.

Epoxy-Chromate(IV) Ester 19 as Possible Intermediates in the Substituent Directed Oxidative Cyclization

In the mechanistic scheme presented earlier (**Scheme IB.2.1**) metallo-oxetane **20** is depicted to be in equilibrium with epoxy chromate(IV) ester **19** which then can undergo oxidative cleavage to lactone **4** via the key intermediate, chromium(IV) ester **6**. Attention was then focussed to find out whether epoxy alcohols of the type **32a-c** would lead to γ-lactones on treatment with oxo-chromium(VI) reagents like PCC. Accordingly γ-epoxy alcohols **32a-c** were prepared by m-chloroperbenzoic oxidation of the corresponding γ-hydroxy olefins **2a-c** (CH_2Cl_2, 25 °C, 1-3h). The crude products obtained in these reactions were used as such for oxidative cyclization studies, although they invariably contained 6-10% of tetrahydrofuran methanol derivatives **30a-c**[43,44]. The crude epoxy alcohols **32a-c** on treatment with pyridinium chlorochromate/molecular sieve 3 A° (CH_2Cl_2, 40°C, 6-8 h) gave the corresponding γ-lactones **4a-c** respectively in good yields (50-65%) (Table **IB.2.2**). This observation again seems to give indirect support to the possibility of the metallo-oxetane **20** and epoxy-chromium(IV) ester **19** as intermediates in the substituent directed oxidative cyclization of **2** to **4**.

Possible Mode of Decomposition of Chromium(IV) Ester 6 to Lactone 4

One aspect which needs further understanding in the mecha-

nistic pathway is the mode of decomposition of the key intermediate chromium(IV) ester **6** to lactone **4**.

Mode 'a' (**Scheme IB.2.3**) suggests a ketone derived enol ether **23** from **6** by elimination which can then undergo oxidative cleavage with excess chromium(VI) reagent to form γ-lactone **4** and formic acid. If this pathway is to be reasonable, then as a general reaction, ketone derived enol ethers should undergo a facile oxidative cleavage with oxo-chromium(VI) reagents. In order to test the validity of this hypothesis a few ketone derived enol ethers **33**, 35, and **37** were prepared (**Chapter IA**). Treatment of **33**, **35**, and **37** with pyridinium chlorochromate (4 mole equiv.) (CH_2Cl_2, 28 °C, 1-2 h) resulted in a smooth conversion of these compounds to lactones **34**, **36**, and **38** respectively in high yields (**Scheme IB.2.6**). These experiments suggest that it is not unreasonable to postulate the intermediacy of enol ethers like **23** in the conversion of **2** to **4** with pyridinium chlorochromate.

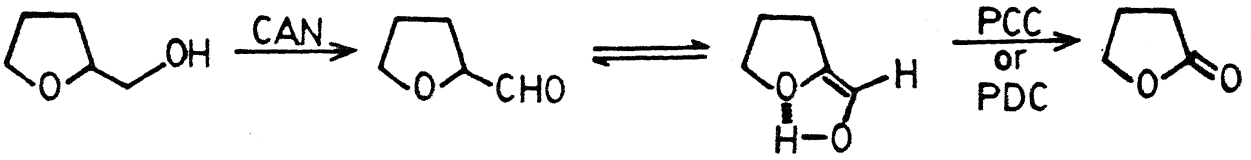
Pathway 'b' (**Scheme IB.2.3**) offers another interesting mode of decomposition of **6** to **4**. This pathway envisages the decomposition of chromium(IV) ester **6** to aldehyde **24** which then can undergo oxidative cleavage <u>via</u> its enol form **24a** with excess oxidant. If this is a reasonable hypothesis then a simple model aldehyde like tetrahydrofurfuraldehyde **29** should undergo oxidative cleavage readily with the chromium(VI) reagent like PCC or PDC. Earlier, it has been shown that oxidation of tetrahydrofurfuryl alcohol **26** under controlled conditions with pyridinium chlorochromate yielded a mixture of lactone **27** and

aldehyde **29** and this aldehyde **29** when independently treated with pyridinium chlorochromate got converted to the lactone **27**. In another experiment pure tetrahydrofurfuraldehyde **29** was prepared separately by oxidation of **26** with ceric ammonium nitrate[45] which on further treatment with pyridinium chlorochromate or pyridinium dichromate (CH_2Cl_2, 40 °C, 3-5 h) yielded the γ-lactone **27** (47-55%) (**Scheme IB.2.7**). Oxidative cleavage of enol of aldehyde with PDC is precedented in the literature[39]. Hence it seems reasonable to postulate that one of the pathways by which chromium(IV) ester **6** decomposes to the lactone **4** may involve an aldehyde intermediate **24**.

Studies on the Attempts to Isolate Intermediates in the Oxidative Cyclization of γ-Hydroxy Olefins with Oxo-Chromium(VI) Reagents

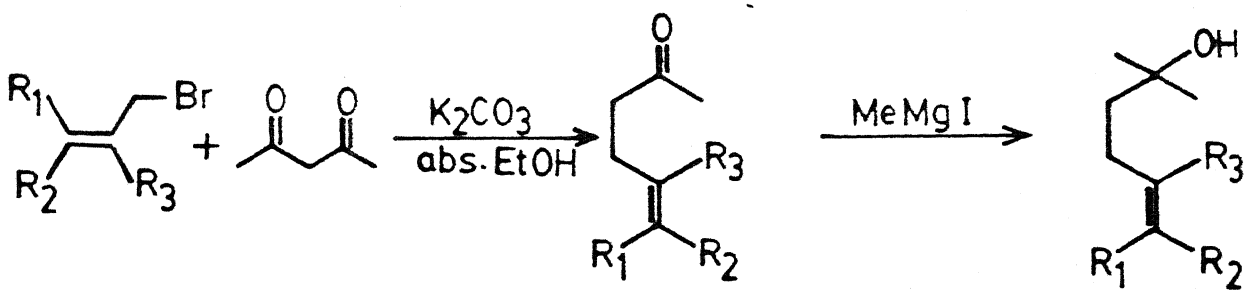
The studies presented thus far have been only on some model compounds similar to postulated intermediates and their conversion to the γ-lactones with chromium(VI) reagents, does not necessarily prove that they are actually the precursors. In order to get some direct evidence about the intermediacy of some of the postulated intermediates, attempts were made to detect/isolate these, if possible, in the reaction of γ-hydroxy olefins with PCC or PDC. For this purpose four different substituted γ-hydroxy olefins **2a, 2d, 2e** and **2i** were prepared[46] as shown in **Scheme IB.2.8. 2a** on treatment with pyridinium chlorochromate/Celite (4 mole equiv.) in dichloromethane under reflux for 48 h, yielded the corresponding lactone **4a** as the only product (53%). On the other hand under controlled conditions (PCC/Celite, 3 mole equiv., Ch_2Cl_2, 30 °C, 6 h) gave a mixture, which on chro-

Scheme-IB-2·7



26 29 27

Scheme-IB-2·8

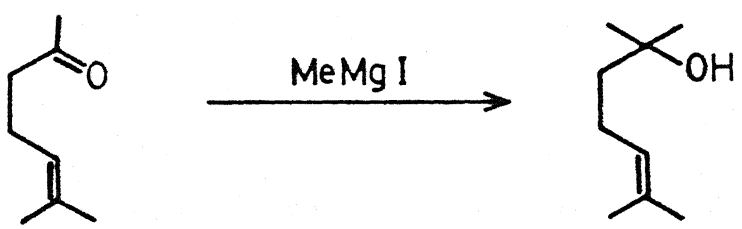


1 2

$R_1 = R_2 = R_3 = H$: a

$R_1 = CH_3$; $R_2 = R_3 = H$: d

$R_1 = R_2 = H$; $R_3 = CH_3$: i

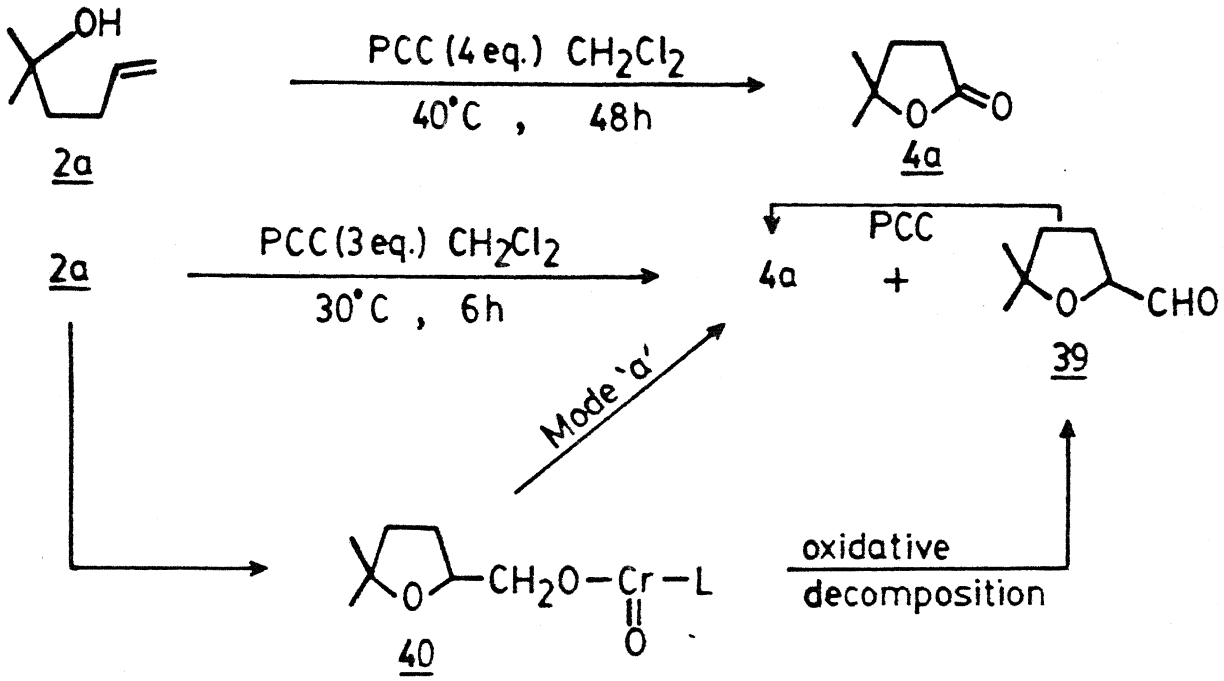


1e 2e

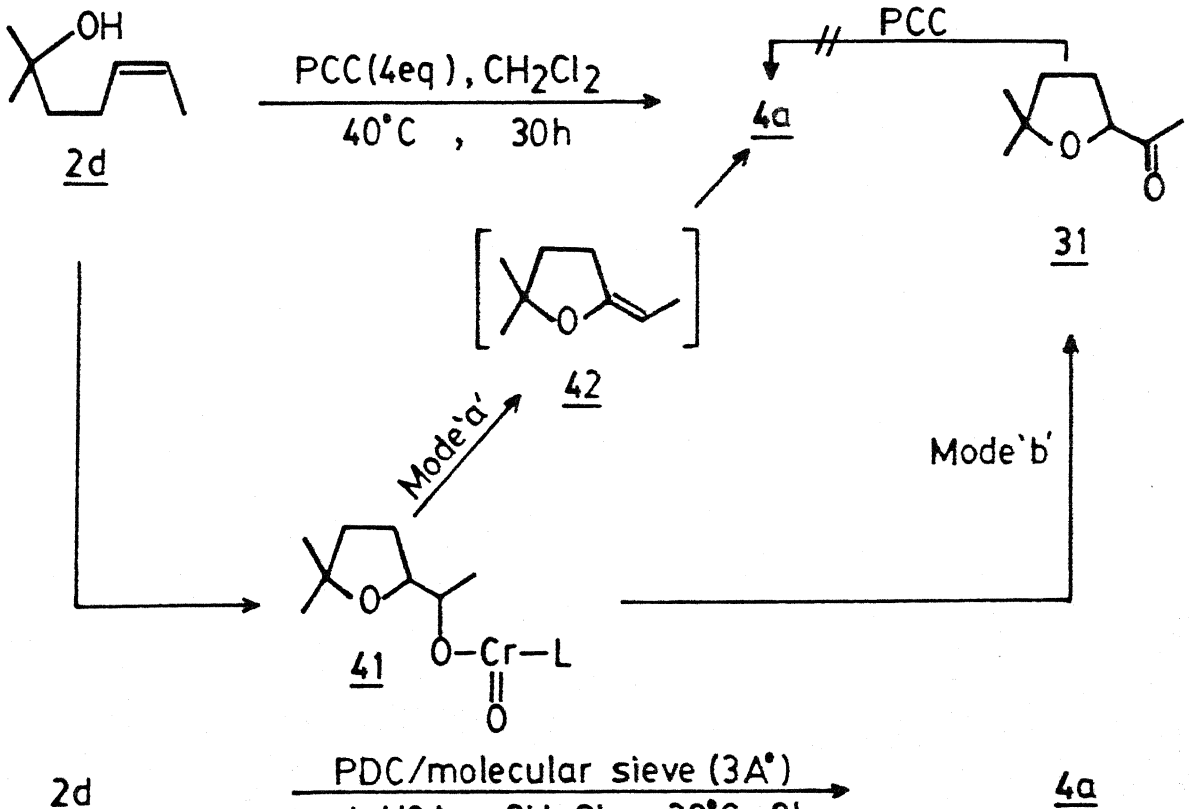
matographic purification yielded the lactone **4a** (20%), the aldehyde **39** (6%) and unreacted starting material (30%). This aldehyde **39** on further treatment with pyridinium chlorochromate/Celite (4 mole equiv., CH_2Cl_2, 40 ^oC, 5 h) afforded the γ-lactone **4a** (**Scheme IB.2.9**). This observation seems to suggest that aldehyde **39** is very likely to be a precursor to **4a** which itself is probably derived from an intermediate **40** similar to chromium(IV) ester **6**.

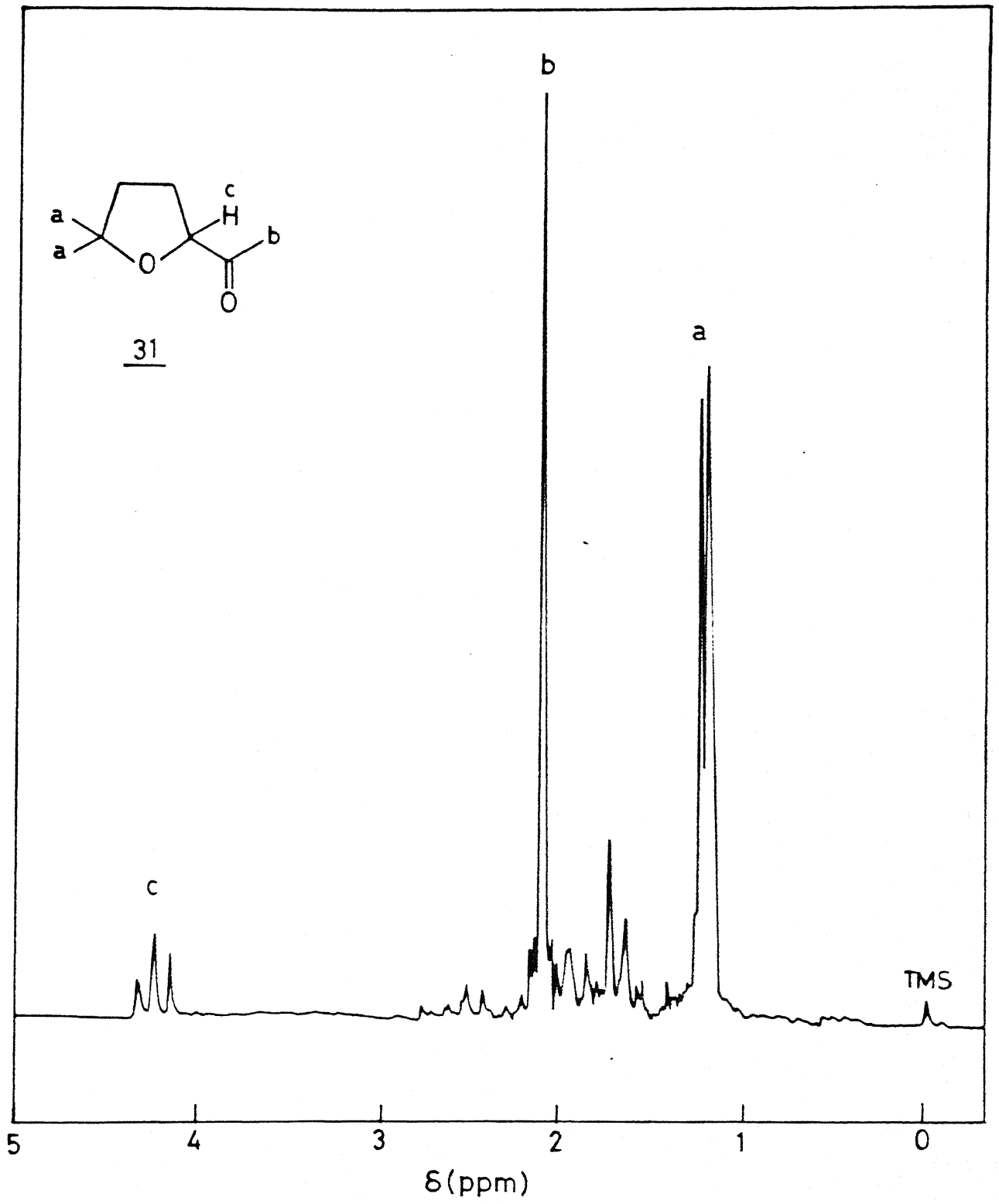
The reaction of γ-hydroxy olefin **2d** with oxo-chromium(VI) reagents provided some interesting information regarding the mechanistic pathway. Treatment of **2d** with pyridinium chlorochromate/Celite (4 mole equiv., CH_2Cl_2, 40 ^oC, 30h) afforded the lactone **4a** (48%) and a highly volatile ketone **31** (7-10%). The same reaction when carried out with pyridinium dichromate activated with molecular sieve 3 A^o [47] containing catalytic amount of acetic acid (CH_2Cl_2, 30 ^oC, 8 h) afforded only the lactone **4a** in good yield (62%) (**Scheme IB.2.10**). The tetrahydrofuran methanol derivative **30d**, derived from **2d**, when treated with PCC/molecular sieve 3 A^o (CH_2Cl_2, 40 ^oC) yielded only the lactone **4a** (57%). On the other hand, **30d** on reaction with Collins' reagent (CrO_3.2Py) in dichloromethane at 0^oC gave the ketone **31** as the only product (78%). This ketone **31** on subsequent treatment with PCC or PDC (4 equiv., 30 ^oC, 48 h) did not give appreciable amounts of lactone **4a** (**Scheme IB.2.11**). This observation indicates that the enolisation of the ketone is not facile and this ketone **31** is not probably an important precursor to **4a**. The formation of lactone **4a** from **30d** or **2d**

Scheme-IB-2·9



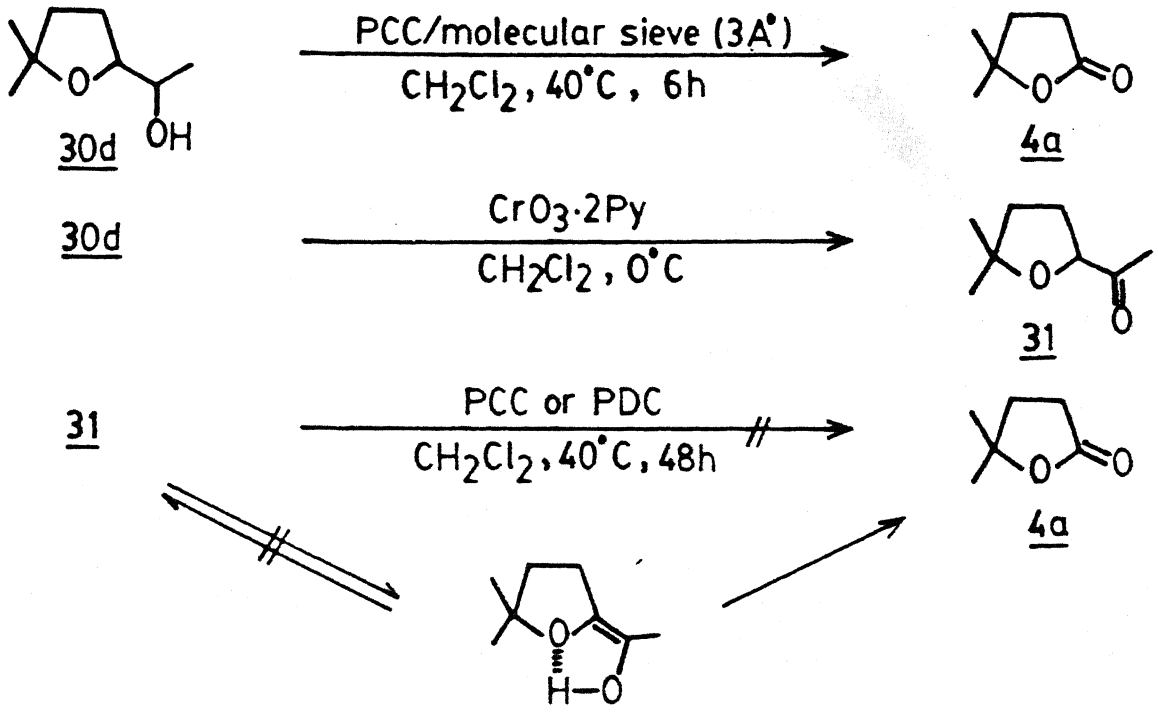
Scheme-IB-2·10



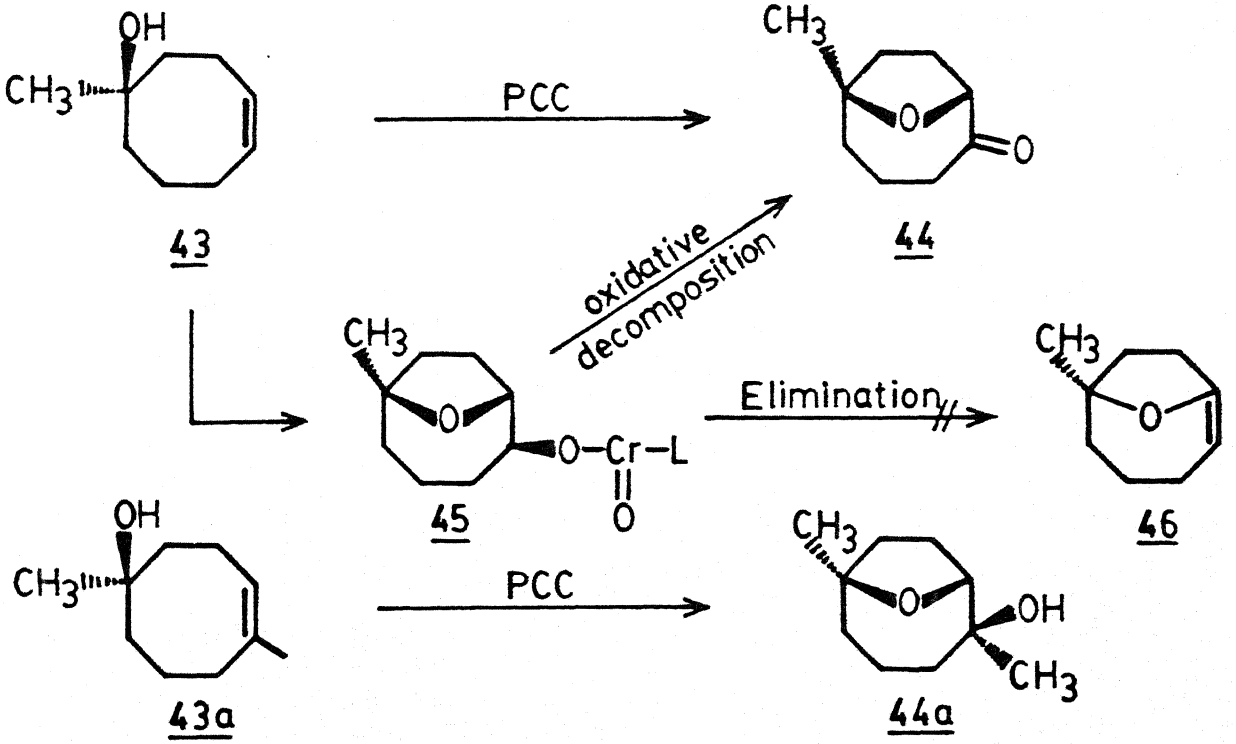


^{1}H NMR Spectrum (80 MHz) of 31

Scheme-IB-2.11



Scheme-IB-2.12

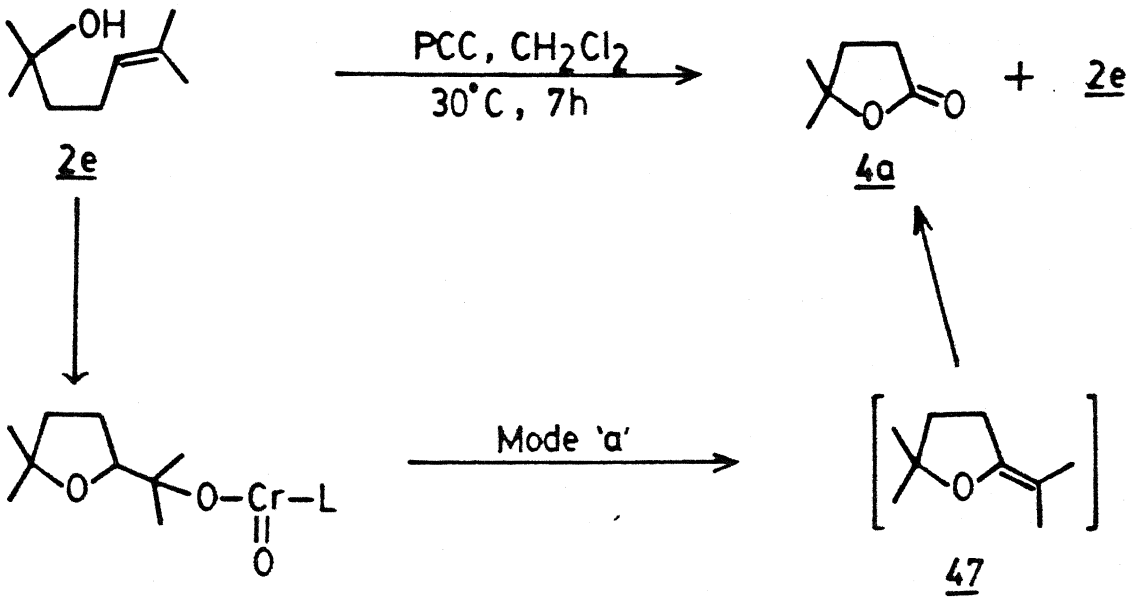


then is more likely to go via an exocyclic enol ether intermediate **42** derived from the chromium(IV) ester **41** by elimination (**Scheme IB.2.10**). As we had shown earlier these exocyclic enol ethers are highly reactive towards PCC or PDC and hence it was difficult to detect or isolate these intermediates from the reaction mixture. This is further supported by a recent report[48] on a substituent directed transannular oxidative cyclization of cyclooctenols to keto -bicyclic ethers with oxo-chromium(VI) reagent (**Scheme IB.2.12**). Cyclooctenol **43** undergoes transannular cyclization with pyridinium chlorochromate to keto-ether **44** via a chromium(IV) ester **45**. This chromate(IV) ester **45** cannot undergo elimination to form enol ether **46** (Bredt's rule). These observations once again support the possible involvement of key intermediate chromium(IV) ester **6** in our reactions also.

As anticipated hydroxy olefin **2e** on treatment with pyridinium chlorochromate (4 mole equiv., 30 ^{o}C, CH_2Cl_2, 7 h) under controlled conditions, yielded the lactone **4a** (18%) and unreacted starting material (49%), but we could not isolate the enol ether intermediate **47** involved in the reaction (**Scheme IB.2.13**).

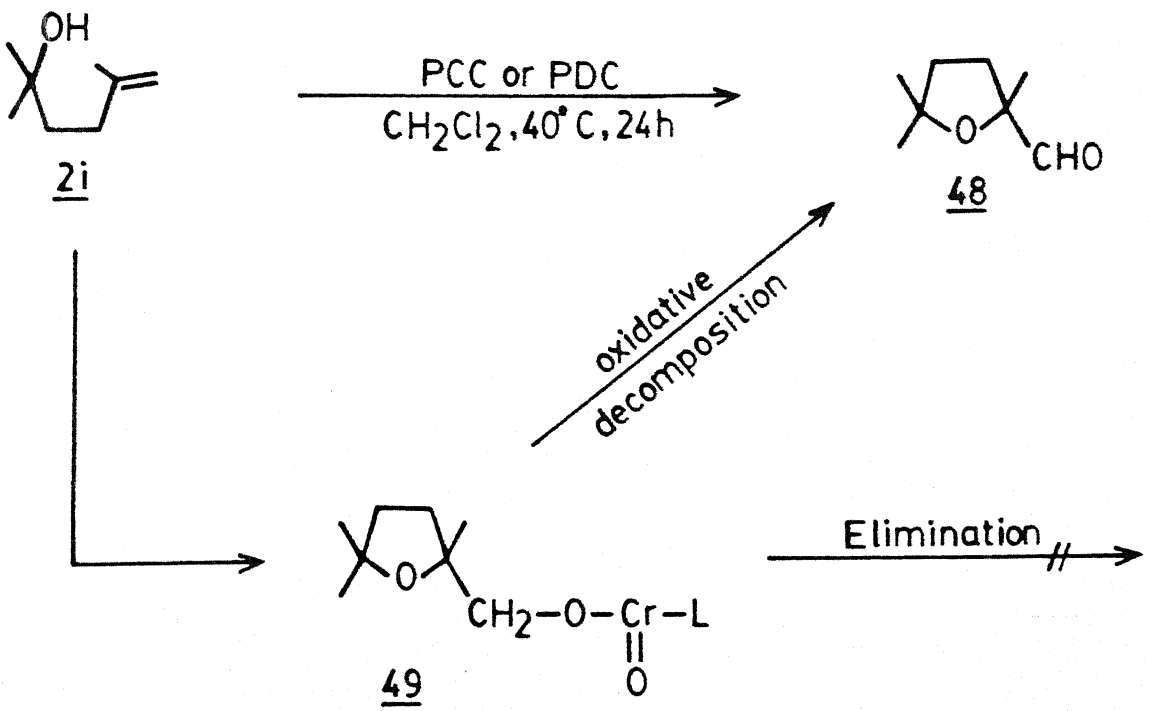
Finally, γ-hydroxy olefin **2i** on treatment with PCC/Celite (4 mole equiv., 40^{o}C, 24 h) or PDC/Celite (4 mole equiv., 40 ^{o}C, 24 h) yielded the corresponding aldehyde **48** as the only product (38%) (**Scheme IB.2.14**). Since the adjacent carbon is a quaternary center, neither the intermediate chromium(IV) ester **49** can undergo elimination to enol ether nor the aldehyde **48** can undergo oxidative cleavage to lactone.

Scheme-IB-2.13

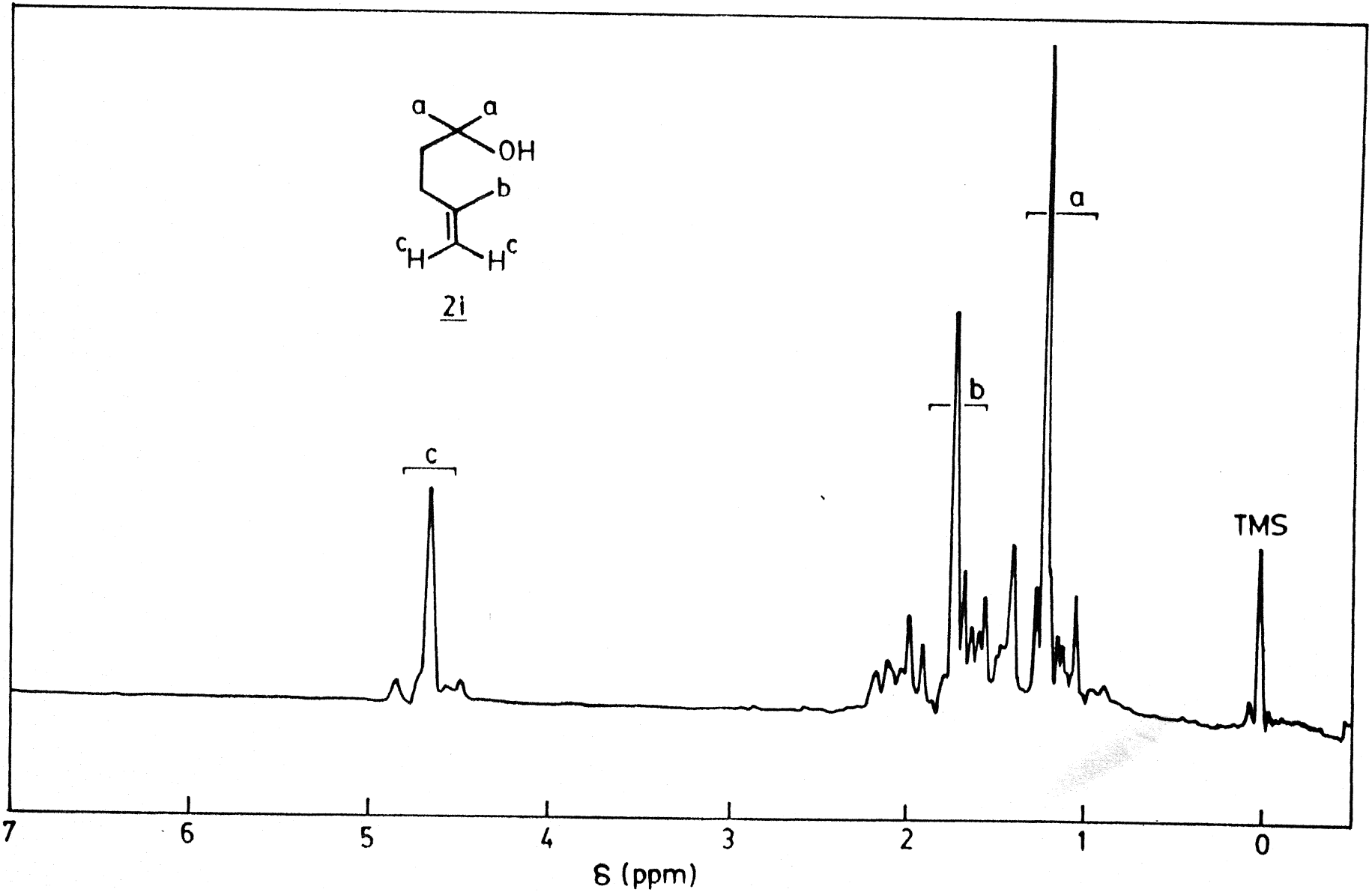


2e 4a 47

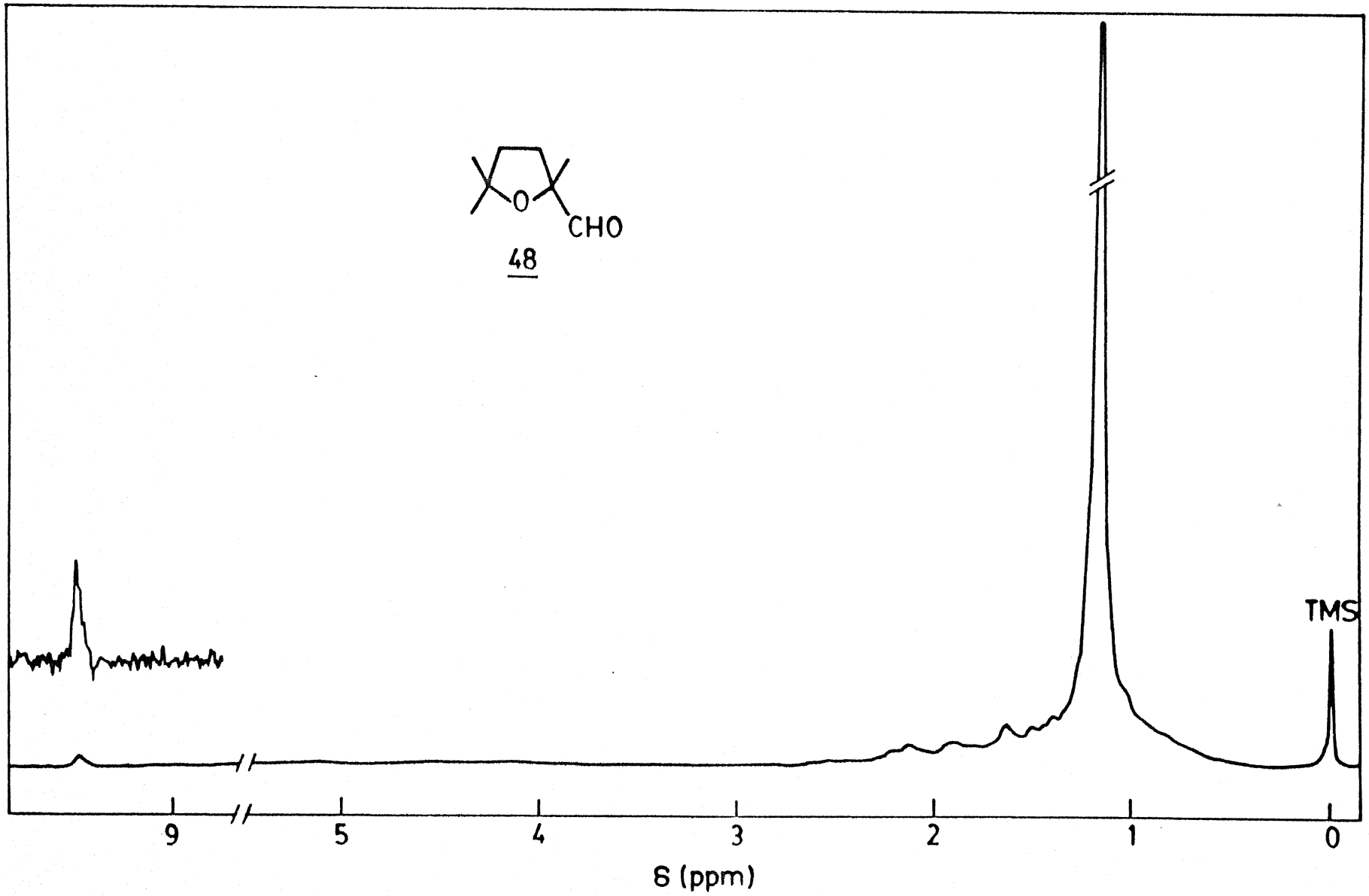
Scheme-IB-2.14



2i 48 49



^{1}H NMR Spectrum (80 MHz) of 2i



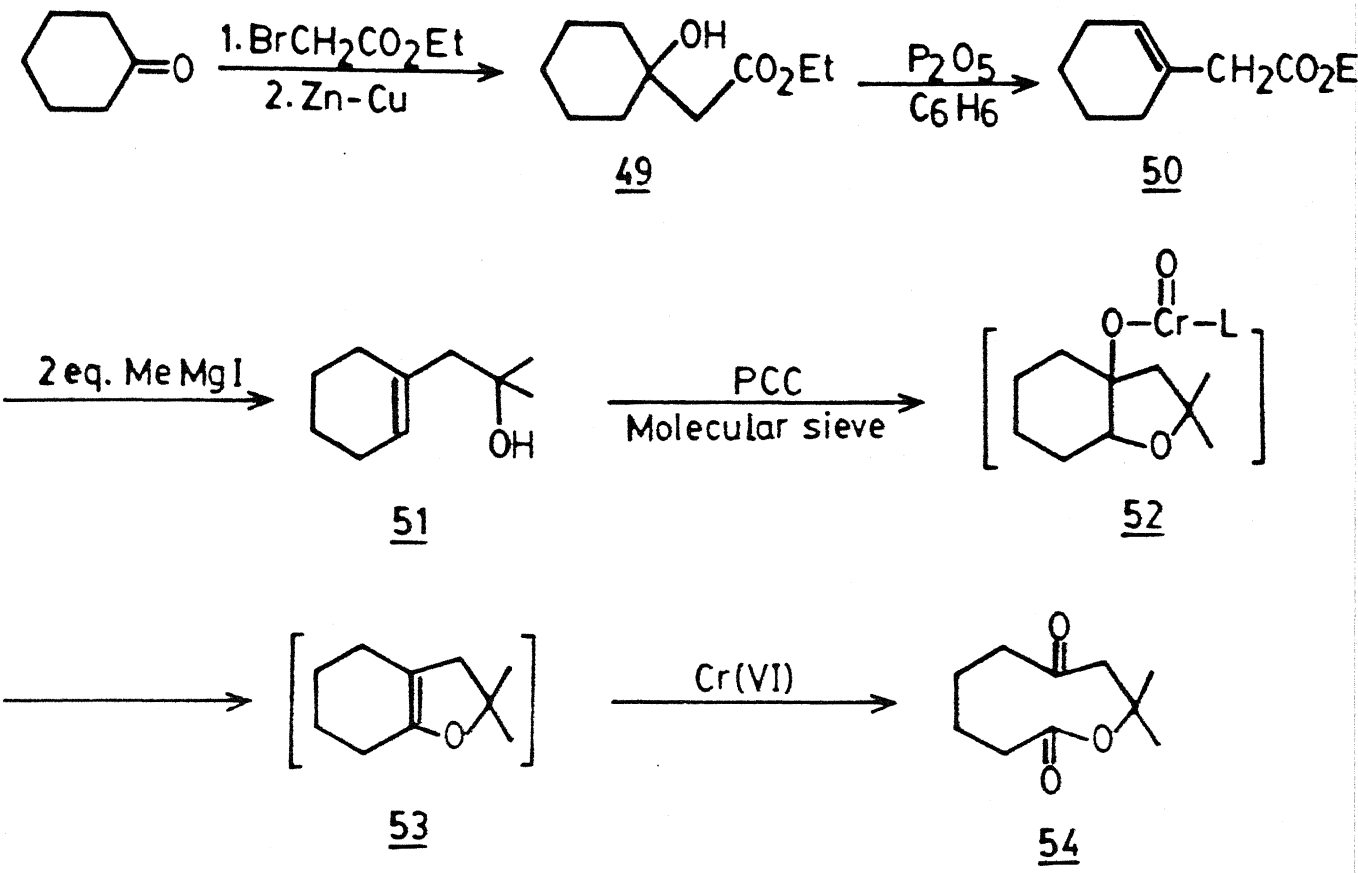
^{1}H NMR Spectrum (90 MHz) of 48

This set of experiments show that, in the oxidative cyclization of γ-hydroxy olefins **2** with oxo-chromium(VI) reagents to γ-lactones **4**, the chromium(IV) ester **6** is very likely to be a key intermediate and the mode of decomposition of **6** to γ-lactones **4** may depend upon the structure of the starting hydroxy olefins **2**. Thus, γ-hydroxy olefins substituted at the terminal carbon of the olefin are likely to give the γ-lactones *via* the formation of exocyclic enol ethers and γ-hydroxy olefins unsubstituted at the terminal carbon of the olefin are likely to produce the corresponding γ-lactones *via* the aldehyde intermediates. It is also clear that in general γ-hydroxy olefins like **2i** having alkyl substituent at the internal carbon of the olefin would not give rise to γ-lactones by an oxidative cleavage process.

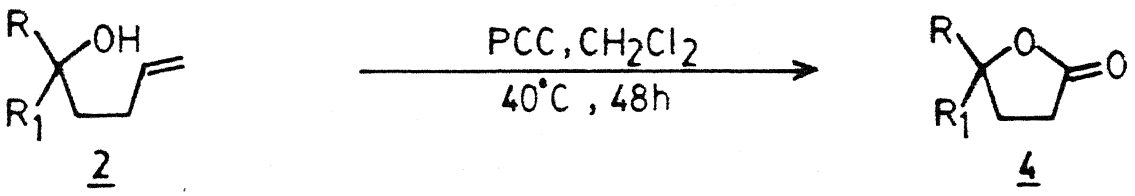
The above proposed mechanism was further supported by an interesting reaction which is shown in **Scheme IB.2.15**. Hydroxy olefin **51** on treatment with PCC/molecular sieves (4 equiv., CH_2Cl_2, 40 °C, 8 h) yielded the ketolactone **54** in 42% yield. It is likely that this reaction goes through the intermediacy of chromium(IV) ester **52** and enol ether 53. It is anticipated that this cyclofunctionalisation methodology would prove to be useful in the synthesis of macrolides.

During the course of our investigation on the mechanism of the substituent directed oxidative cyclization of γ-hydroxy olefins to γ-lactones, we realized that the oxidative cyclization reaction is much faster under acidic and anhydrous conditions. Under neutral conditions, reaction is slower and under basic conditions, reaction is very sluggish. By

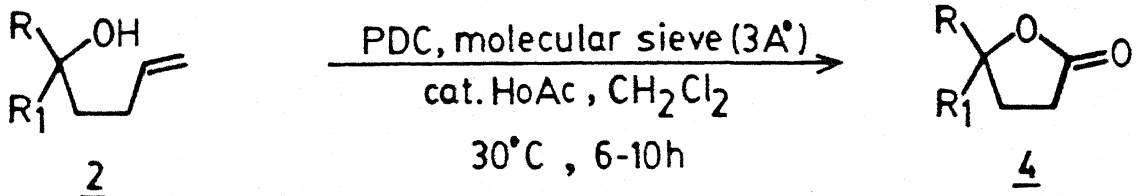
Scheme-IB-2·15

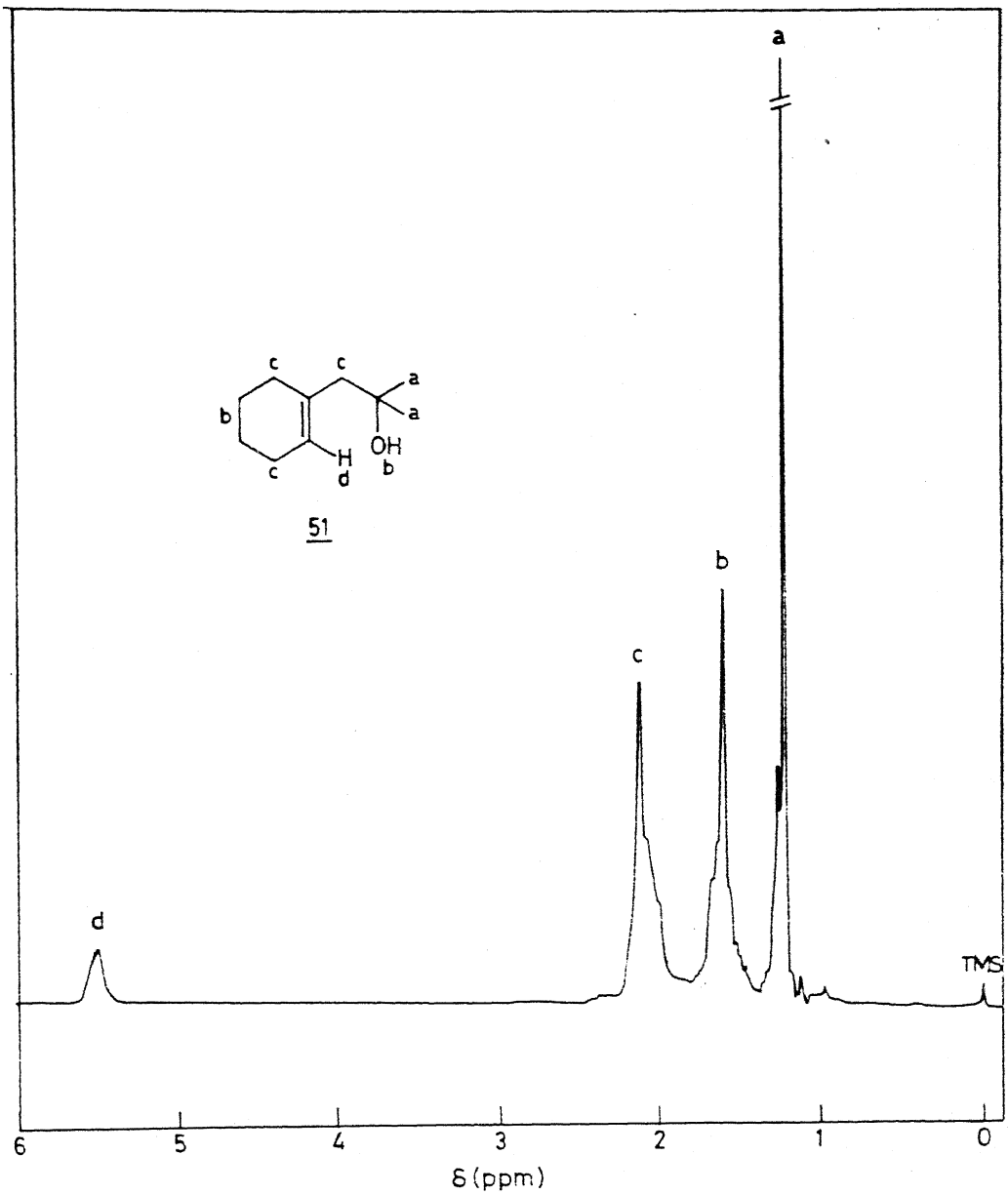


Scheme-IB-2·16



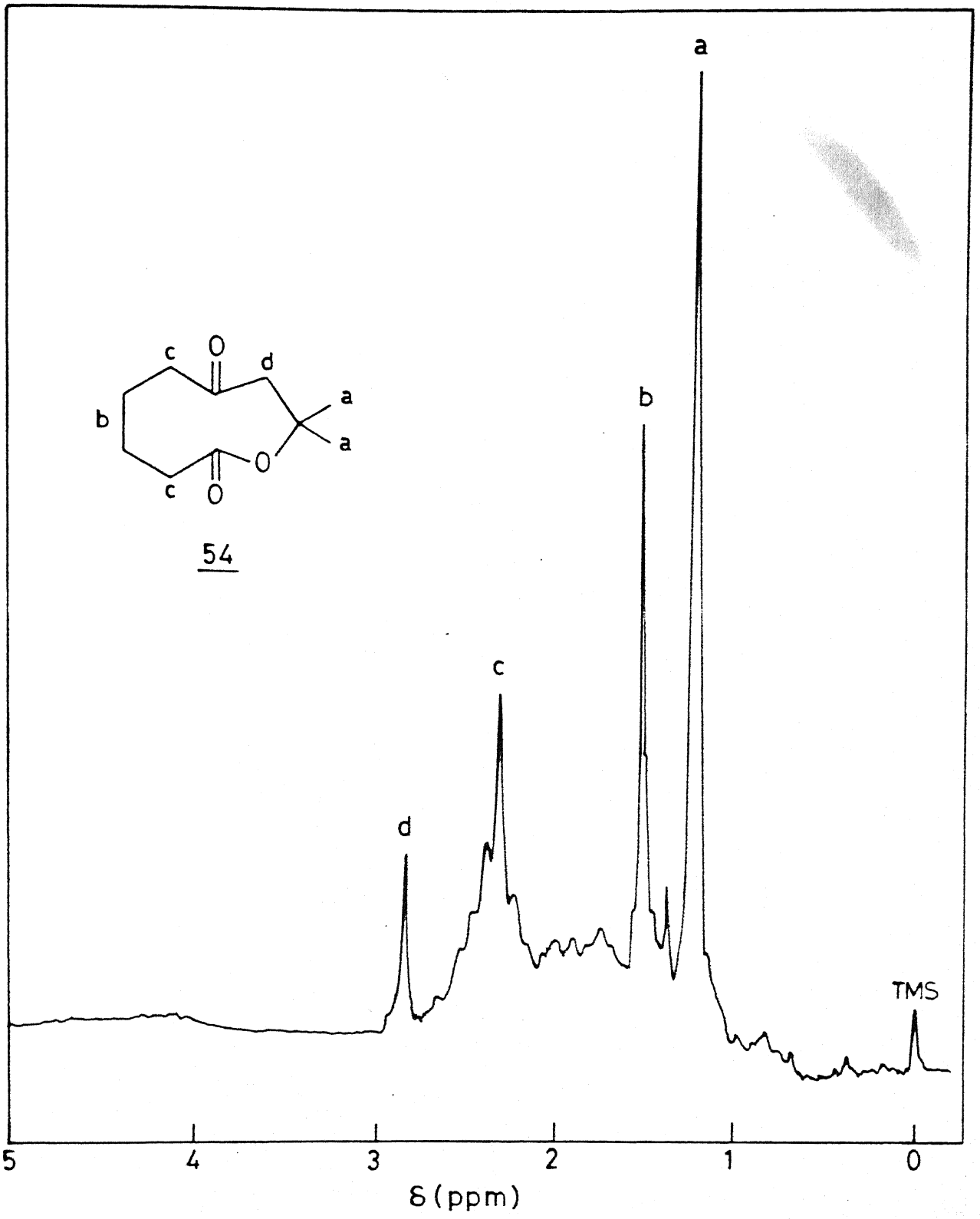
MODIFIED PROCEDURE :





51

^{1}H NMR Spectrum (80 MHz) of 51



54

^{1}H NMR Spectrum (80 MHz) of 54

considering the above mentioned factors, we modified the earlier reported[12] procedure for the substituent directed oxidative cyclization of γ-hydroxy olefins **2** to γ-lactones **4** (**Scheme IB.2.16**).

All the four pathways suggested for the formation of key intermediate chromium(IV) ester **6** are likely and we have been able to get some evidence for the operation of path **'A'** and path **'B'**. Both the modes of decomposition of the key intermediate chromium(IV) ester **6** are possible and depend upon the substituents on the alkene.

In summary, the mechanism that we have suggested accounts for most of our observations and throws some light on the course of this substituent directed oxidative cyclization process, although there is no conclusive evidence in its favour.

IB.3 EXPERIMENTAL

General Procedure

As described in Chapter IA.

Materials

As described in Chapter IA.

Chromatograpy

As given in Chapter IA.

Physical Data

As given in Chapter IA.

Preparation of Hex-5-en-2-one 1a[46,49,50]

A mixture of acetylacetone (11.0 g, 0.11 mol), freshly

distilled allyl bromide (12.1 g, 0.1 mol) and anhydrous potassium carbonate (16.0 g, 0.115 mol) in absolute ethanol (60 mL) was refluxed for 18 h. Ethanol (50 mL) was distilled off, the residue was cooled and ice-cold water (120 mL) was added to dissolve all the salt and extracted with ether. Ether extracts were dried over anhydrous ($MgSO_4$), solvent was evaporated and the crude product was distilled to get hex-5-en-2-one **1a**[46] (5.6 g, 57%), b.p. 126-7 ^oC (lit.[46] b.p. 129 ^oC).

IR (neat) : 3080, 1715, 1640 cm^{-1}

^1H NMR ($CDCl_3$) : δ 2.14 (s, 3 H), 2.24-2.64 (m, 4 H), 4.9-5.14 (m, 2 H), 5.6-6.04 (m, 1 H).

Preparation of Hept-5-en-2-one 1d[49,51]

To a stirred mixture of acetylacetone (11.0 g, 0.11 mol) and anhydrous potassium carbonate (16.0 g, 0.115 mol) in absolute ethanol (60 mL) was added crotyl chloride (9.06 g, 0.1 mol) and the resulting mixture was refluxed for 18 h to yield hept-5-en-2-one **1d**[49] (8.85 g, 79%), b.p. 148-150 ^oC (lit.[49] b.p. 148-152 ^oC).

IR (neat) : 3030, 1720, 1660 cm^{-1}

^1H NMR ($CDCl_3$) : δ 1.63 (d, 3 H), 2.07 (s, 3 H), 2.16-2.45 (m, 4 H), 5.34-5.53 (sext, 2 H).

Preparation of 5-Methyl-hex-5-en-2-one 1i[46,49]

Freshly distilled acetylacetone (1.1 g, 11 mmol) was treated with 2-methyl-3-bromo-prop-1-ene (1.35 g, 10 mmol) and anhydrous potassium carbonate (1.6 g, 11.5 mmol) for 18 h under reflux, as described earlier to give 5-methyl-hex-5-en-2-one

1i[46] (0.694 g, 62%) after chromatographic purification on silica gel (1:10, ether-petroleum ether 40-60 °C), b.p. 148-9 °C (lit.[46] b.p. 148-149 °C).

IR (neat) : 3060, 1715, 1660 cm^{-1}

^1H NMR ($CDCl_3$) : δ 1.66 (s, 3 H), 2.06 (s, 3 H), 2.19-2.46 (m, 4 H), 4.5 (s, 2 H).

Addition of Methyl Magnesium iodide to Hex-5-en-2-one 1a[52]

Methyl magnesium iodide was prepared from freshly distilled methyl iodide (1.7 g, 12 mmol) and magnesium turnings (0.288 g, 12 mg atom) in dry ether (10 mL). It was cooled with ice cold water and hex-5-en-2-one (0.98 g, 10 mmol) in dry ether (5 mL) was added to it dropwise with stirring. After the addition was over, it was stirred for additional 1 h and then worked up by slow addition of excess of saturated aqueous ammonium chloride solution and extracted with ether. Ether extracts were dried over anhydrous $MgSO_4$ and the solvent was evaporated to get **2a**[52] as an oil (1.11 g, 97%)

IR (neat) : 3380, 3070, 1640 cm^{-1}

^1H NMR ($CDCl_3$) : δ 1.25(s, 6 H), 1.44-1.66 (m, 3 H), 2.0-2.31 (m, 2 H), 4.87-5.13 (m, 2 H), 5.63-6.13 (m, 1 H).

MS (m/e) : 99 (M^+-15), 83, 59.

Addition of Methyl Magnesium iodide to 1d[53]

Methyl magnesium iodide, derived from methyl iodide (1.7 g, 12 mmol) and magnesium turnings (0.288 g, 12 mg atom) was treated with hept-5-en-2-one **1d** (1.12 g, 10 mmol) as described earlier to yield **2d**[53] (1.23 g, 96%) after chromatographic

purification on silica gel (1:10, ether-petroleum ether).

IR (neat) : 3450, 3080, 1645 cm^{-1}

^1H NMR ($CDCl_3$) : δ 1.22 (s, 6 H), 1.38-1.53 (m, 3 H), 1.63 (d, 3 H), 1.97-2.19 (m, 2 H), 5.34-5.53 (sext, 2 H).

Preparation of 2e[53]

Methyl magnesium iodide, derived from methyl iodide (1.7 g, 12 mmol) and magnesium turnings (0.288 g, 12 mg atom) was treated with 6-methyl-hept-5-en-2-one **1e** (1.26 g, 10 mmol) as described above, to yield **2e**[53] (1.349 g, 95%) after chromatographic purification on silica gel (1:10, ether-petroleum ether).

IR (neat) : 3460, 3090, 1670 cm^{-1}

^1H NMR ($CDCl_3$): δ 1.22 (s, 6 H), 1.44-1.59 (m, 2 H), 1.66 (br,d, 6 H), 1.90-2.19 (m, 3 H), 5.30-5.22 (t, 1 H).

Preparation of 2i[54]

Methyl magnesium iodide, prepared from methyl iodide (0.85 g, 6 mmol) and magnesium turnings (0.144 g, 6 mg atom) in dry ether was treated with 5-methyl-hex-5-en-2-one **1i** (0.56 g, 5 mmol) and the resulting mixture was stirred for 1h. The crude product obtained after the usual work-up was purified by flash chromatography on silica gel (1:10, ether-petroleum ether) to afford **2i**[54] (0.589 g, 92%) as a colorless oil.

IR (neat) : 3470, 3060, 1650 cm^{-1}

^1H NMR ($CDCl_3$): δ 1.22 (s, 6 H), 1.38-1.53 (m, 3 H), 1.72 (s,

3 H), 1.86-2.06 (m, 2 H), 4.63 (s, 2H).

General Procedure for the Oxidation of Hydroxy Olefins to Tetrahydrofuran Methanol Derivatives

Oxidation of 2a with m-Chloroperbenzoic Acid[55]

To a stirred solution of **2a** (0.456 g, 4 mmol) in chloroform (10 mL) at 0 °C was added m-chloroperbenzoic acid (0.863, 5 mmol) and the resulting mixture was stirred at 0 °C for 24 h. The reaction mixture was poured into ice-water and the organic phase was washed with aqueous sodium carbonate solution, water, and then with brine. Then solvent was dried over $MgSO_4$ and evaporated under reduced pressure. The crude product after chromatographic purification on silica gel (1:10, ethyl acetate-petroleum ether) yielded tetrahydrofuran methanol **30a**[55] (0.322 g, 62%) as a colorless oil.

IR (neat) : 3460, 1160-1040 cm^{-1}

^1H NMR ($CDCl_3$): δ 1.17 (s, 6 H), 1.57-1.88 (m, 4 H), 2.03 (br,s, 1 H), 3.26-3.47 (m, 2 H), 3.8-4.07 (m, 1 H).

MS (m/e) : 129 (M^+-1), 115, 99.

Preparation of Tetrahydrofuran Methanol Derivate 30b

γ-Hydroxy olefin **2b** (0.56 g, 4 mmol) was treated with m-chloroperbenzoic acid (0.863 g, 5 mmol) in chloroform (10 mL) at 0 °C for 24 h as described earlier, to get tetrahydrofuran methanol **30b** (0.418 g, 67%) as a colorless oil.

IR (neat) : 3450, 1160-1040 cm^{-1}

^1H NMR ($CDCl_3$) : δ 1.53-1.72 (m, 8 H), 1.78-2.01 (m, 5 H), 3.32-3.48 (m, 2 H), 3.83-4.02 (m, 1 H).

MS (m/e) : 155 (M^+-1), 125.

Preparation of 30c

γ -Hydroxy olefin **2c** (0.616 g, 4 mmol) was allowed to react with m-chloroperbenzoic acid (0.863 g, 5 mmol) in chloroform (10 mL) at 0 °C for 24 h and **30c** (0.442 g, 65%) was obtained as a colorless oil, after chromatographic purification on silica gel (1:10, ethylacetate-petroleum ether).

IR (neat) : 3450, 1160-1040 cm^{-1}

^1H NMR ($CDCl_3$) : δ 1.41-1.53 (m, 10 H), 1.82-2.13 (m, 5 H), 3.44-3.65 (m, 2 H), 4.06-4.18 (m, 1 H).

MS (m/e) : 169 (M^+-1), 139.

Preparation of 30d[43]

γ-Hydroxy olefin **2d** (0.512 g, 4 mmol) was treated under similar reaction conditions with m-chloroperbenzoic acid (0.863 g, 5 mmol) in chloroform for 24 h. Tetrahydrofuran methanol derivative **30d**[43] (0.415 g, 72%) was obtained after chromatographic purification on silica gel (1:10, ethyl acetate-petroleum ether).

IR (neat) : 3420, 1180-1040 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.12 (d, 3 H), 1.28 (s, 6 H), 1.72-1.96 (m, 4 H), 2.68 (br,s, 1 H), 3.84-4.08 (m, 2 H).

MS (m/e) : 144 (M^+), 129, 99, 81.

Preparation of 30e[43]

γ-Hydroxy olefin **2e** (0.568 g, 4 mmol) in chloroform (10 mL) was treated with m-chloroperbenzoic acid (0.863 g, 5 mmol) at 0 °C for 15 h, to afford **30e**[43] (0.493 g, 78%) as a colorless

oil, after chromatographic purification.

IR (neat) : 3450, 1180-1040 cm^{-1}

^1H NMR ($CDCl_3$) : δ 1.13, 1.19 (2s, 6 H), 1.25 (s, 6 H), 1.59-1.88 (m, 4 H), 2.78 (br,s, 1 H), 3.69-3.88 (m, 1 H)

MS (m/e) : 143 (M^+-15), 141, 99.

Preparation of 30f[43,56]

γ-Hydroxy olefin **2f** (0.816 g, 4 mmol) was reacted with m-chloroperbenzoic acid (0.863 g, 5 mmol) in chloroform (10 mL) at 0 °C for 9 h, under similar conditions, to yield **30f**[43] (0.669 g, 76%) as an oil

IR (neat) : 3420, 3060, 1610, 1170 - 1030 cm^{-1}

^1H NMR ($CDCl_3$) : δ 1.12, 1.16 (2s, 3 H), 1.28 (s, 3 H), 1.48, 1.50 (2s, 3 H), 1.68-2.24 (m, 5 H), 3.68-4.04 (2t, 1 H), 7.14-7.46 (m, 5 H).

MS (m/e) : 219 (M^+-1), 205, 162, 161, 143, 118, 59.

Preparation of 30g:

γ-Hydroxy olefin **2g** (0.872 g, 4 mmol) upon treatment with m-chloroperbenzoic acid (0.863 g, 4 mmol) in chloroform (10 mL) at 0 °C for 7 h, yielded tetrahydrofuran methanol derivative **30g** (0.861 g, 92%) as an oil, after chromatographic purification on silica gel (1:10, ethyl acetate-petroleum ether)

IR (neat) : 3450, 3060, 1600, 1140-1050 cm^{-1}

^1H NMR($CDCl_3$) : δ 1.04 (s, 3 H), 1.24, 1.28 (2s, 6 H), 1.64-1.92 (m, 5 H), 2.88 (d, 2 H), 3.60-3.96 (m, 1 H), 7.28 (s, 5 H).

MS (m/e) : 217 (M^+-17), 143, 91, 43

Preparation of 30h[40,43]:

To a solution of linalool **2h** (0.617 g, 4 mmol) was added m-chloroperbenzoic acid (0.690 g, 4 mmol) in chloroform (10 mL) at 0 °C for 8 h. Tetrahydrofuran methanol **30h**[40] (0.490 g, 72%) was obtained after chromatographic purification on silica gel (1:10, ethyl acetate-petroleum ether).

IR (neat) : 3460, 3100, 1640, 1160, 1000 cm^{-1}

^1H NMR($CDCl_3$) : δ 1.12 (s, 3 H), 1.24 (s, 3 H), 1.32(s, 3 H), 1.76-1.97 (m, 4 H), 2.22 (br,s, 1 H), 3.52-3.84 (m, 1 H), 4.92-5.28 (m, 2 H), 5.72-6.12 (m, 1 H)

MS(m/e) : 155 (M^+-15), 111, 94, 59, 43.

General Procedure for the Oxidation of Tetrahydrofuran Methanols with PCC/Molecular sieves

Oxidation of 30a

Powdered molecular sieves (3 A°) (1.7 g) was heated under N_2 at 320 °C with a Bunsen burner for 1 h. It was allowed to come to room temperature and pyridinium chlorochromate (1.7 g, 8 mmol) and dry dichloromethane (10 mL) were added. To this mixture was added a solution of **30a** (0.26 g, 2 mmol) in dichloromethane (5 mL) and stirred under reflux for 8 h. Diethyl ether (50 mL) was added and it was filtered through a short pad of Celite and silica gel. The filter cake was washed thoroughly with ether (2x30 mL) and the filtrate was concentrated. The residue after flash chromatography (1:2, ether-petroleum ether afforded **4a**[57] (0.121 g, 53%) as an oil.

IR (neat) : 1780 cm^{-1}

^{1}H NMR ($CDCl_3$) : δ 1.4 (s, 6 H), 1.8-2.27 (m, 2 H), 2.4-2.85 (m, 2 H).

MS (m/e) : 114 (M^+), 99, 70, 55, 43, 39.

Oxidation of 30b with PCC/Molecular sieves

Treatment of **30b** (0.312 g, 2 mmol) with pyridinium chlorochromate (1.72 g, 8 mmol) and molecular sieves (1.7 g), under the conditions described above, yielded **4b**[58,59] (0.162 g, 58%) as a liquid after chromatographic purification.

IR (neat) : 1775 cm^{-1}

^{1}H NMR ($CDCl_3$) : δ 1.3-1.8 (m, 8 H), 1.9-2.1 (m, 2 H), 2.5-2.7 (t, 2 H).

MS (m/e) : 140 (M^+), 112, 98, 96, 56.

Oxidation of 30c :

Tetrahydrofuran methanol **30c** (0.34 g, 2 mmol) was treated with pyridinium chlorochromate (1.72 g, 8 mmol) and molecular sieves (1.7 g) in dry dichloromethane (15 mL) under reflux for 8 h as described earlier to give lactone **4c**[58-60] (0.166 g, 54%) as a colorless oil.

IR (neat) : 1775 cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ 1.3-1.8 (m, 10 H), 2.0 (t, 2 H), 2.5-2.6 (t, 2 H).

MS (m/e) : 154 (M^+), 126, 112, 110, 56.

Oxidation of 30d with PCC/Molecular sieves

A mixture of pyridinium chlorochromate (1.72 g, 8 mmol) and molecular sieves (1.7 g) in dichloromethane (10 mL) was treated with **30d** (0.288 g, 2 mmol) in dichloromethane (5 mL). The

resulting mixture was stirred under reflux for 7 h to yield lactone **4a**[57] (0.130 g, 57%) after chromatographic purification. Lactone **4a** was found to be identical with an authentic sample.

Oxidation of 30e with PCC/molecular sieves

Tetrahydrofuran methanol **30e** (0.316 g, 2 mmol) was treated with pyridinium chlorochromate (1.72 g, 8 mmol) and molecular sieves (1.7 g) in dichloromethane (15 mL) under reflux for 6 h as described earlier to give lactone **4a**[57] (0.143 g, 63%), which was found to be identical with an authentic sample.

Oxidation of 30f with PCC/Molecular sieves

Treatment of **30f** (0.440, 2 mmol) with pyridinium chlorochromate (1.72 g, 8 mmol) and molecular sieves (1.7 g) in dichloromethane (15 mL) under reflux for 4h, yielded lactone **4f**[56,58,61] (0.289 g, 82%) after chromatographic purification.

IR (neat) : 3080, 1775, 1600 cm^{-1}

^1H NMR ($CDCl_3$) : δ 1.72 (s, 3 H), 2.35-2.69 (m, 4 H), 7.3 (s, 5 H).

MS (m/e) : 176 (M^+), 161, 105, 77.

Oxidation of 30g with PCC/Molecular sieves

To a mixture of pyridinium chlorochromate (1.72 g, 8 mmol) and molecular sieves (1.7 g) in dichloromethane (10 mL) was added a solution of **30g** (0.468 g, 2 mmol) in dichloromethane (5 mL) and the resulting mixture was stirred under reflux for 3 h. The crude product after chromatographic purification, yielded lactone **4g**[62] (0.361 g, 95%) as an oil.

IR(neat) : 3080, 3060, 1770, 1600 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.44 (s, 3 H), 1.91-2.15 (m, 2 H), 2.16-2.27 (m, 1 H), 2.35-2.5 (m, 1 H), 2.94 (d, 2 H, J = 3.75 Hz), 7.21-7.35 (m, 5 H).

MS (m/e) : 190 (M^+), 135, 100, 91

Oxidation of 30h with PCC/Molecular sieves

Tetrahydrofuran methanol **30h** (0.34 g, 2 mmol) was treated with pyridinium chlorochromate (1.72 g, 8 mmol) and molecular sieves (1.7g) in dichloromethane (15 mL) under reflux for 4 h as described earlier, to yield lactone **4h**[40,63] (0.184 g, 73%) after chromatographic purification.

IR(neat) : 3090, 1780, 1650 cm^{-1}

^1H NMR($CDCl_3$) : δ1.43 (s, 3 H), 1.89-2.20 (m, 2 H), 2.31-2.56 (m, 2 H), 5.03-5.33 (m, 2 H) 5.73-6.04 (m, 1 H).

MS (m/e) : 126 (M^+), 111, 55, 43.

Preparation of Epoxy Alcohol 32a

To a stirred solution of **2a** (0.456 g, 4 mmol) in chloroform (10 mL) at 25 °C was added m-chloroperbenzoic acid (1.035 g, 6 mmol) and the resulting mixture was stirred at 25 °C for 3 h. The reaction mixture was poured into ice-water and the organic phase was washed sequentially with aqueous sodium carbonate solution, water and then with brine. The solvent was dried over $MgSO_4$ and evaporated under reduced pressure. The crude product **32a** (0.302 g, 58%) was used as such in the oxidation reaction with pyridinium chlorochromate/molecular sieves.

IR(neat) : 3460, 1120-1040 cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ 1.17 (s, 6 H), 1.53-1.86 (m, 4 H), 2.03 (br,s, 1 H), 2.53-2.9 (m, 3 H).

Preparation of Epoxy Alcohol 32b

γ -Hydroxy olefin **2b** (0.56 g, 4 mmol) was treated with m-chloroperbenzoic acid (1.035g, 6 mmol) in chloroform (10 mL) at 25 °C for 2 h, as described earlier, to get epoxy alcohol **32b** (0.312 g, 50%) as a colorless oil.

IR (neat) : 3400, 1120-1030 cm^{-1}.

^{1}H NMR($CDCl_3$) : δ 1.52-1.84 (m, 12 H), 1.9(br,s, 1 H), 2.47-2.94 (m, 3 H).

Preparation of Epoxy Alcohol 32c

γ -Hydroxy olefin (0.616 g, 4 mmol) was allowed to react with m-chloroperbenzoic acid (1.035 g, 6 mmol) in chloroform (10 mL) at 25 °C for 2 h as above to yield epoxy-alcohol **32c** (0.374 g, 55%) as an oil.

IR (neat) : 3450, 1120-1040 cm^{-1}.

^{1}H NMR($CDCl_3$) : δ 1.42-1.53 (m, 10 H), 1.57-1.98 (m, 5 H), 2.53-3.02 (m, 3 H).

Reaction of 32a with PCC/Molecular sieves

Powdered molecular sieves (3A°) (1.7 g) was heated under N_2 at 320 °C with a Bunsen burner for 1 h. It was allowed to come to room temperature and pyridinium chlorochromate (1.72 g, 8 mmol) and dry dichloromethane (10 mL) were added. To this mixture was added a solution of **32a** (0.26 g, 2 mmol) in dichloromethane (5 mL) and stirred under reflux for 8 h. Diethyl

ether (50 mL) was added and it was filtered through a short pad of Celite and silica gel. The filter cake was washed thoroughly with ether (2x30 mL) and the filtrate was concentrated. The residue after flash chromatography (1:2, ether-petroleum ether) afforded **4a**[57] (0.114 g, 50%), which was found to be identical with an authentic sample.

Reaction of 32b with PCC/Molecular sieves

A mixture of pyridinium chlorochromate (1.72 g, 8 mmol) and molecular sieves (1.2 g) in dichloromethane (15 mL) was treated as earlier with **32b** (0.312 g, 2 mmol) for 6 h under reflux to yield lactone **4b**[58,59] (0.182 g, 65%) after flash chromatography. Spectral data were found to be identical with that of an authentic sample.

Reaction of 32c with PCC/Molecular sieves

Epoxy alcohol **32c** (0.340 g, 2 mmol) was allowed to react with pyridinium chlorochromate (1.72 g, 8 mmol) and molecular sieves (1.7 g) in dichloromethane (15 mL) for 8 h under reflux. The crude product after flash chromatography,yielded lactone **4c**[58-60] (0.181 g, 59%) as an oil. Spectral data were found to be identical with that of an authentic sample.

Oxidation of Tetrahydrofurfuryl Alcohol 26 with PCC

To a stirred mixture of pyridinium chlorochromate (2.15 g, 10 mmol) and Celite (2.1 g) in dry dichloromethane (15 mL) was added a solution of **26** (0.204 g, 2 mmol) in dichloromethane (2 mL) and the resulting reaction mixture was stirred under reflux

for 5 h. It was then cooled to room temperature, diluted with ether (50 mL) and filtered through a pad of Celite and silica gel. The filter cake was washed with ether and the filtrate was concentrated. The crude product was purified by flash chromatography on silica gel (1:10, ethyl acetate-petroleum ether) to give the aldehyde **29**[64] (0.012 g, 6%).

IR(CCl_4) : 2720, 1715 cm^{-1}

^1H NMR ($CDCl_3$) : δ 1.8-2.0 (m, 4 H), 3.7-4.2 (m, 3 H), 9.6 (s, 1 H).

MS (m/e) : 100 (M^+), 71, 39.

Further elution (1:5, ethyl acetate-petroleum ether) afforded the butyrolactone **27** (0.088g, 51%)

IR ($CHCl_3$) : 1775 cm^{-1}

^1H NMR($CDCl_3$) : δ 2.03-2.4 (m, 4 H), 4.17-4.3 (t, 2 H).

MS (m/e) : 86 (M^+).

Oxidation of 26 with PCC Under Controlled Conditions

A mixture of pyridinium chlorochromate (1.72 g, 8 mmol) and Celite (1.7 g) in dry dichloromethane (10 mL) was treated with **26** (0.204 g, 2 mmol) in dichloromethane (2 mL) at room temperature (28 ^oC)for 5 h to yield the aldehyde **29**[64] (0.02 g, 10%), lactone **27** (0.017 g, 10%) and unreacted starting material **26** (0.081 g, 40%) after chromatographic purification. Spectral data were found to be identical to the one reported earlier.

Oxidation of 26 with PDC

A mixture of pyridinium dichromate (3.76 g, 10 mmol) and Celite (3.7 g) in dichloromethane (20 mL) was treated with **26** (0.204 g, 2 mmol) in dichloromethane (2 mL) and the resulting

mixture was stirred under reflux for 6 h. The crude product, after chromatographic purification, yielded the aldehyde **29**[64] (0.02 g, 10%) and the lactone **27** (0.079 g, 46%).

Oxidation of 26 with Ceric Ammonium Nitrate

To a solution of tetrahydrofurfuryl alcohol **26** (1.02 g, 10 mmol) in acetonitrile (25 mL) was added ceric ammonium nitrate (10.0 g) and it was stirred overnight at room temperature. The reaction mixture was extracted with ether (60 mL) and washed with water and brine solution. The ether extract was dried ($MgSO_4$) and the solvent was evaporated. The residue was distilled to give **29**[64] (0.62 g, 62%) b.p. 140 °C (lit[64] b.p. 140 °C).

IR(CCl_4) : 2720, 1715 cm^{-1}.

^1H NMR($CDCl_3$) : δ 1.8-2.0 (m, 4 H), 3.7-4.2 (m, 3 H), 9.6 (s, 1 H).

MS (m/e) : 100 (M^+), 71, 39.

Oxidation of Tetrahydofurfural 29 with PCC

Treatment of **29** (0.2 g, 2 mmol) with pyridinium chlorochromate (1.72g, 8 mmol) and Celite (1.7 g) in dichloromethane (10 mL) under refulx for 3h, yielded the lactone **27** (0.095 g, 55%) after chromatographic purification. Spectral data were found to be identical with an authentic sample.

Oxidation of Aldehyde 29 with PDC

A mixture of pyridinium dichromate (3.0 g, 8 mmol) and Celite (3.0 g) in dichloromethane (15 mL) was treated with **29** (0.2 g, 2 mmol) in dichloromethane (2 mL) and the resulting

IR ($CHCl_3$) : 1780 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.4 (s, 6 H), 1.8-2.1 (m, 2 H), 2.4-2.7 (m, 2 H).

MS (m/e) : 114 (M^+), 99 , 70, 55, 43, 39.

Oxidation of 2a with PCC Under Controlled Conditions

Treatment of **2a** (0.228 g, 2 mmol) with pyridinium chlorochromate (1.29 g, 6 mmol) and Celite (1.3g) in dichloromethane (10 mL) at 30°C for 6 h yielded, after chromatographic purification, the aldehyde **39** (0.015g, 6%),

IR ($CHCl_3$) : 2720, 1720 cm^{-1}

^1H NMR ($CDCl_3$) : δ 1.20 (2s, 6 H), 1.56-1.92 (m, 4 H), 4.24 (m, 1 H), 9.4 (s, 1 H).

MS (m/e) : 128, 113, 99, 39

the lactone **4a**[57] (0.046 g, 20%) and unreacted starting material **2a** (0.068 g, 30%).

Oxidation of Aldehyde 39 with PCC

A mixture of **39** (0.013 g, 0.1 mmol), pyridinium chlorochromate (0.086 g, 0.4 mmol) and Celite (0.08 g) in dichloromethane (2 mL) was stirred under reflux for 5 h. The crude product after chromatographic purification yielded lactone **4a**[57] (0.005 g, 49%), spectral data were found to be identical with an authentic sample.

Oxidation of 2d with PCC

γ-Hydroxy olefin **2d** (0.256 g, 2 mmol) was treated with pyridinium chlorochromate (1.72 g, 8 mmol) and Celite (1.7 g) in

dichloromethane under reflux for 30 h. The crude product was purified by flash chromatography on silica gel (1:10, ethyl acetate-petroleum ether) to give the ketone **31**[43] (0.02 g, 7%).

IR (neat) : 1705, 1150-1070 cm^{-1}

^1H NMR ($CDCl_3$) : δ 1.19 (s, 3 H), 1.22 (s, 3 H), 1.53-1.93 (m, 4 H), 2.09 (s, 3 H), 4.13-4.31 (t, 1 H).

MS (m/e) : 142, 127, 99, 81, 43.

Further elution (1:5, ethyl acetate-petroleum ether) yielded the lactone **4a**[57] (0.109 g, 48%).

Oxidation of 30d with CrO_3.2Py

To a solution of distilled pyridine (3.12 g, 40 mmol) in dry dichloromethane (25 mL) was added chromium trioxide (2.0 g, 20 mmol) and dry Celite (1.5 g). The resulting mixture was stirred at room temperature for 0.25 h. To the cooled burgundy red homogeneous solution of the reagent at 0 °C was added a solution of **30d** (0.288 g, 2 mmol) in dichloromethane (2 mL). The reaction mixture turned black immediately and then it was stirred at 0 °C for an additional 1 h. The reaction mixture was diluted with ether (50 mL), filtered through a pad of Celite and sand and the filter cake was washed thoroughly with ether. The filtrate was evaporated and the crude product was purified by flash chromatography on silica gel (1:10, ether-petroleum ether) to yield the ketone **31**[43] (0.222 g, 78%) as an oil, b.p. 73-75 °C/12 mm (lit.[43] b.p. 75 °C/12 mm).

IR(neat) : 1705, 1150-1070 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.19 (s, 3 H), 1.22 (s, 3 H), 1.53-1.93 (m, 4 H), 2.09 (s, 3 H), 4.13-4.31 (t, 1 H).

MS (m/e) : 142, 127, 99, 81, 43.

Oxidation of Keto-ether 31 with PCC

Keto-ether **31** (0.142 g, 1 mmol), PCC (0.86 g, 4 mmol) and Celite (0.8 g) in dichloromethane were refluxed for 48 h. After the usual work-up, the starting material keto-ether **31** (0.128 g, 90%) was recovered unchanged.

Oxidation of 2e with PCC Under Controlled Conditions

A mixture of pyridinium chlorochromate (1.72 g, 8 mmol) and Celite (1.7 g) in dry dichloromethane (10 mL) at 30 °C was treated with **2e** (0.284 g, 2 mmol) in dichloromethane (2 mL) and the resulting mixture was stirred at 30 °C for 7 h. After the usual work-up, the crude product was purified by flash chromatography on silica gel (1:5, ethyl acetate-petroleum ether) to yield the lactone **4a**[57] (0.041 g, 18%) and unreacted starting alcohol **2e** (0.140 g, 49%). Lactone **4a** and alcohol **2e** were found to be identical in all respects with the authentic samples

Oxidation of 2i with PCC

Treatment of **2i** (0.256 g, 2 mmol) with pyridinium chloro chromate (1.72 g, 8 mmol) and Celite (1.7 g) in dichloromethane (15 mL) under reflux for 24 h, yielded the aldehyde **48** (0.11 g, 42%) after chromatographic purification on silica gel (1:10, ether-petroleum ether).

IR ($CHCl_3$) : 2720, 1715 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.2 (br,s, 9 H), 1.52-2.12 (m, 4 H), 9.44 (s, 1 H).

MS (m/e) : 142, 127, 113

Oxidation of 2i with PDC:

A mixture of **2i** (0.256 g, 2 mmol), pyridinium dichromate (3.0 g, 8 mmol) and Celite (3.0 g) was refluxed for 24 h to yield the aldehyde **48** (0.110g, 39%) after flash chromatography. Spectral data were found to be identical with that of the compound obtained by PCC oxidation of **2i**.

Modified Procedure for the Oxidation of Hydroxy olefins to Lactones

Oxidation of 2a with PDC

Powdered molecular sieves (3 A^{O}) (3.0g) was heated under N_2 at 320 ^{O}C with a Bunsen burner for 1 h. It was allowed to come to room temperature and pyridinium dichromate (3.76 g, 10 mmol) and anhydrous acetic acid (200 μL) in dichloromethane (15 mL) were added. To this mixture was added a solution of **2a** (0.228 g, 2 mmol) in dichloromethane (2 mL) and stirred at 30 ^{O}C for 10 h. Ether (40 mL) was added and it was filtered through a short pad of Celite and silica gel. The filter cake was washed with ether (2x30 mL) and the filtrate was concentrated. The residue after flash chromatography (1:5, ethyl acetate-petroleum ether) afforded **4a**[57] (0.130 g, 57%)

Oxidation of 2b with PDC:

Treatment of **2b** (0.28 g, 2 mmol) with pyridinium dichromate (3.76 g, 10 mmol), molecular sieves (3.0 g) and acetic acid (200μL) at 30^{O}C for 6 h, yielded the lactone **4b**[58,59] (0.182 g,

65%) after chromatographic purification.

IR ($CHCl_3$) : 1775 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.3-1.8 (m, 8 H), 1.9-2.1 (m, 2 H), 2.5-2.7 (t, 2 H).

MS (m/e) : 140 (M^+), 112, 98, 96, 56.

Oxidation of 2c with PDC :

A mixture of **2c** (0.308 g, 2 mmol) pyridinium dichromate (3.76 g, 10 mmol), molecular sieves (3.0 g) and acetic acid (200 μL) was stirred at 30 °C for 8 h, under similar conditions as described earlier, to give **4c**[58-60] (0.185 g, 60%) as a colorless oil.

IR(CCl_4) : 1775 cm^{-1}.

^1H NMR($CDCl_3$) : δ 1.3-1.8 (m, 10 H), 2.0 (t, 2 H), 2.5-2.6 (t, 2 H).

MS (m/e) : 154(M^+), 126, 112, 110, 56

Oxidation of 2d with PDC

A mixture of pyridinium dichromate (3.76 g, 10 mmol), molecular sieves (3.0 g) and acetic acid (200 μL) in dichloromethane (15 mL) was treated with **2d** (0.256 g, 2 mmol) at 30 °C for 8 h to yield the lactone **4a**[57] (0.141 g, 62%) after chromatographic purification.

Preparation of 49[66] by Reformatsky Reaction

The Zn-Cu couple was prepared before use from granulated zinc (3 g) and copper(II) acetate hydrate [$Cu(OAC)_2.H_2O$; 0.3 g] in acetic acid (5 mL) with stirring at room temperature (28 °C)

for 0.5 h. The acetic acid was then decanted and the couple was washed with dry ether (3x10 mL) and benzene (10 mL). To the Zn-Cu couple, dry THF (5 mL) was added with vigorous stirring and then a solution of cyclohexanone (1.96 g, 20 mmol) and ethyl bromoacetate (4.2 g, 25 mmol) in THF (10 mL) was added dropwise in such a manner as to keep the mixture at gentle reflux. After the addition was over, the mixture was refluxed for 1 h, then allowed to come to room temperature and acidified with 5 N sulfuric acid and extracted with ether (3x20 mL). The extract was dried over $MgSO_4$, the solvent was evaporated and the crude product was purified by distillation under vacuum to yield **49**[66] (3.05 g, 82%) b.p. 84 ^{o}C/1 mm (lit.[66] b.p. 86-89 ^{o}C/2mm).

IR(neat) : 3460, 1735 cm^{-1}

Conversion of 49 to 50

Ethyl 1-cyclohexanol acetate (2.5 g) was dissolved in dry benzene (10 mL) and P_2O_5 (2.0 g) was added to the solution. The mixture was refluxed on a water-bath for 3 h and allowed to come to room temperature. The benzene solution was decanted, the porous residue was rinsed twice with benzene (25 mL) and the combined organic layers were dried over $MgSO_4$. The benzene was removed under reduced pressure and the crude product was distilled under vacuum to yield the unsaturated ester **50**[67] (1.536 g, 68%) b.p 93-95 ^{o}C/10 mm (lit.[67] b.p. 100 ^{o}C / 12 mm).

IR (neat) : 3090, 1735, 1670 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 1.16-1.34 (t, 3 H), 1.5-1.72 (m, 4 H), 1.91-2.16 (m, 6 H), 2.88 (s, 2 H), 3.97-4.22 (q, 2 H), 5.53 (br,s, 1 H).

Reaction of 50 with Methyl Magnesium iodide

Methyl magnesium iodide was prepared from freshly distilled methyl iodide (1.7 g, 12 mmol) and magnesium turnings (0.288 g, 12 mg atom) in dry ether (15 mL). It was cooled with ice-water and **50** (0.84 g, 5 mmol) in dry ether (5 mL) was added dropwise with stirring. After the addition was over, it was stirred for additional 3 h at room temperature and then worked up by slow addition of excess of saturated aqueous ammonium chloride solution and then extracted with ether. Ether extracts were dried over anhydrous $MgSO_4$, solvent was evaporated and the crude product was purified by flash chromatography on silica gel (1:10, ethyl acetate-petroleum ether) to yield the hydroxy olefin **51** (0.647 g, 84%) as an oil.

IR (neat) : 3450, 3090, 1670 cm^{-1}

^1H NMR ($CDCl_3$): δ 1.22 (s, 6 H), 1.59 (br,s, 5 H), 2.09 (br,s, 6 H), 5.5 (br,s, 1 H).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.92; H, 11.69.
Found: C, 77.98; H, 11.72.

Oxidation of 51 with PCC/Moleular sieves

Powdered molecular sieves (3 A^o) (1.7 g) was heated under N_2 at 320 ^oC with a Bunsen burner for 1h. It was allowed to come to room temperature and pyridinium chlorochromate (1.72 g, 8 mmol) and dry dichloromethane (10 mL) were added. To this mixture was added a solution of **51** (0.308 g, 2 mmol) in dichloromethane (5 mL) and stirred under reflux for 8 h. Ether (50 mL) was added and it was filtered through a short pad of

Celite and silica gel. The filter cake was washed thoroughly with ether (2x30 mL) and the filtrate was concentrated. The residue, after flash chromatography (1:2, ether-petroleum ether) yielded **54** (0.155 g, 42%).

IR ($CHCl_3$) : 1740, 1715 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.22 (s, 6 H), 1.53 (s, 4 H), 2.22-2.50 (m, 4 H), 2.81 (s, 2 H).

MS (m/e) : 184 (M^+), 129, 111, 98, 83, 53.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.22; H, 8.69.

Found: C, 65.31; H, 8.71.

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CHAPTER IIA

OXIDATIVE TRANSFORMATION WITH OXO-MANGANESE(VII) REAGENTS HETEROGENEOUS PERMAGANATE OXIDATION OF OLEFINS: A OMEGA PHASE CATALYSIS

IIA.1 INTRODUCTION

Permanganate Oxidation Under Homogeneous Conditions

Potassium permanganate, an oxidizing agent used in organic chemistry for over a century,[1] is one of the most versatile and vigorous of the commonly used oxidants. It has been extensively employed in acid, alkaline and neutral media. The use of permanganate as a selective oxidant for a variety of reactions has been reviewed by Stewart,[2] Arndt,[3] Freeman,[4] Waters,[5] Lee[6] and Fatiadi.[7]

Aqueous permanganate has found its greatest application in the oxidation of organic compounds containing polar groups that provide them with at least partial solubility in water.[2] The classical way of overcoming the solubility problem has been by use of polar organic solvent systems that would dissolve both reactants. Obviously, the use of organic solvent system is limited to the oxidation of those compounds that react much more readily with permanganate than the solvent itself.[6]

Although potassium permanganate is a powerful oxidizing agent, its utility in organic synthesis has been severely

limited by its poor solubility in non-polar solvents.[7] However, the observation that potassium permanganate could be extracted from water into benzene by use of phase transfer agents[8] substantially increases the potential usefulness of this reagent.

Permanganate ion solubilized in benzene or dichloromethane by use of quaternary ammonium salts,[8,9] dimethyl poly(ethyleneglycol)[10] or cryptates,[11] is an effective new reagent; the oxidation here is conducted under anhydrous or almost anhydrous conditions. Quaternary phosphonium and arsonium salts can also be used as phase transfer agents.[12] The effectiveness of any particular phase transfer system will be dependent on the ability of that system to bring the permanganate ion into solution in the organic phase. This phase transfer technique has been applied extensively to a variety of synthetic procedures in addition to oxidation reactions. Numerous review articles[8,13] and books[14] on the subject are available.

Oxidation of Alkenes

In aqueous solution, permanganate readily oxidizes water soluble alkenes.[2] The nature of the products is however, dependent on the reaction conditions. In acidic solution, cleavage reaction predominates,[15a] under basic conditions dihydroxylation is the main reaction [15b] and in neutral medium ketols are formed as the major products.[16] Unfortunately the conditions under which these reactions take place are not sharply defined and mixtures of products are often obtained.

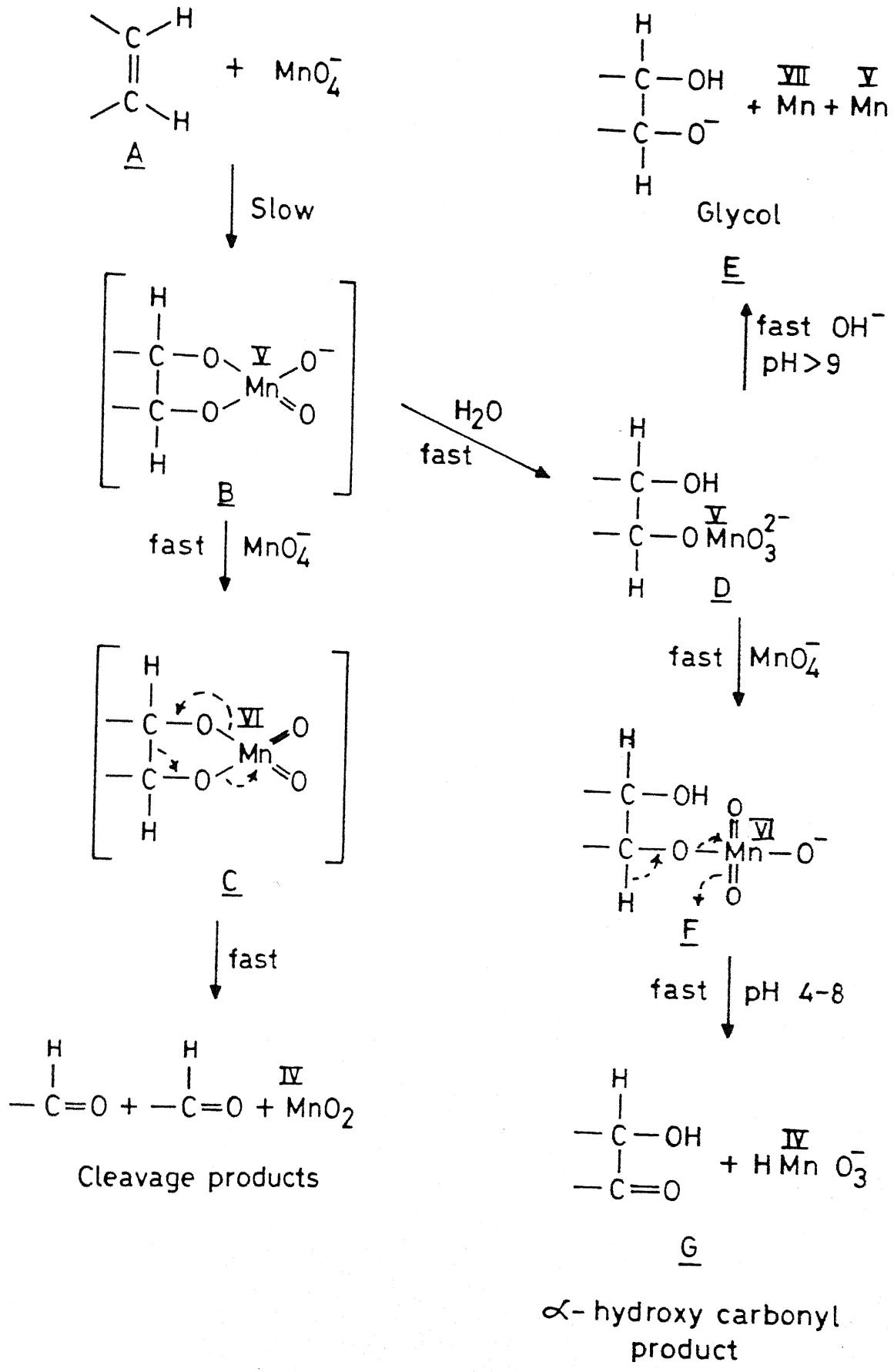
There is a general agreement that cyclic manganese esters are formed in the initial step of the oxidation of alkenes.[2,17] It has been found that during the dihydroxylation reaction, the two hydroxy groups are added cis,[18] and that the oxygen atoms are transferred directly from the MnO_4^- ion.[19] More recently, species having only transient life times, believed to be intermediate manganese(V) esters, have been detected by using stop-flow techniques.[20]

Mechanism of Permanganate Oxidation of Alkenes

The nature of short-lived intermediates in the permanganate oxidation of unsaturated compounds has recently received considerable attention.[4,21] The most recent work[22] discusses at length the possible intermediacy of cyclic hypomanganate-[manganese(V)] ester during the oxidation of carbon-carbon double bond.

As shown in **Scheme IIA.1.1**, the initial stage of the reaction may involve a [3+2] electrocyclic addition of permanganate ion to the alkenic π-bond in **A**, to afford the cyclic manganate(V) ester **B**.[4,22a,23] Manganate(V) ester **B** may undergo hydrolysis to an α-glycol **E** [via an acyclic manganese(V) ester **D**] or oxidative hydrolysis to an α-ketol **G** [via an acyclic manganese(VI) ester **F**], depending on the pH. Rapid oxidation of **B** to the manganese(VI) ester **C** by electron transfer and subsequent fragmentation of **C** may proceed via [2+2+2] chelotropic change,[9a] to give cleaved products. The glycol **E** is a major product at pH > 9 (cyclic alkenes)[24] or pH > 12 (acyclic alkenes).[7] The ketol **G** is a major product in the pH

Scheme-IIA-1.1



range of 4 to 8, but is not formed *via* the glycol.[22c]

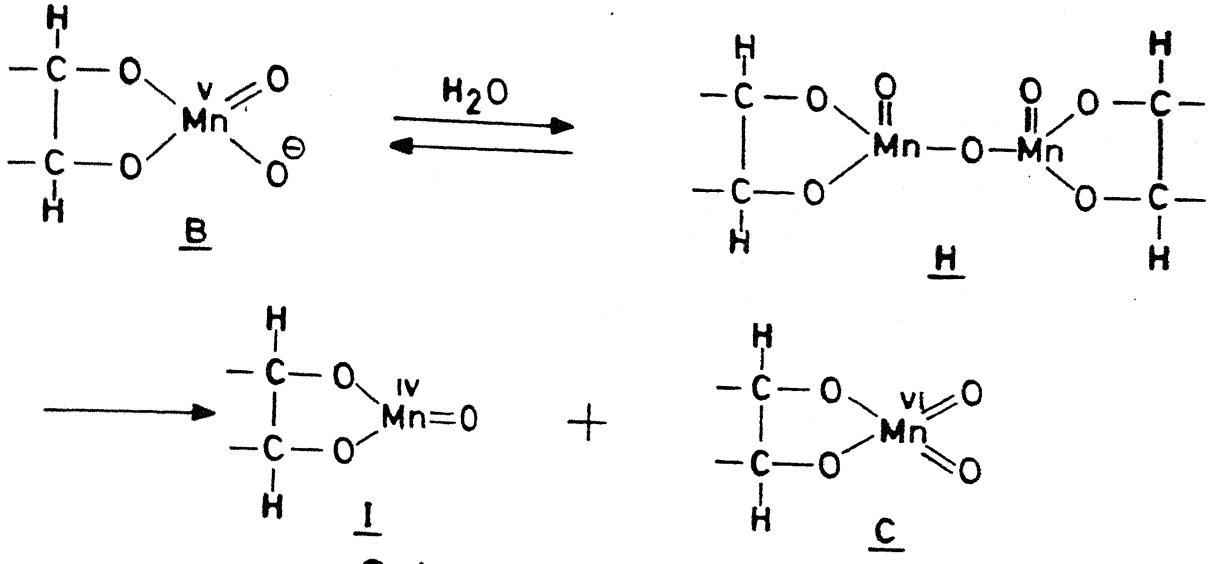
On the basis of stereochemistry of the reaction,[25] ^{18}O-labeling experiments[19] and kinetic studies, the cyclic manganate(V) ester **B** is considered to be an intermediate in the formation of glycol and to undergo hydrolysis with fission of the Mn-O bonds. The kinetic results support the view that the glycol and the ketol are formed from a common intermediate.

The transformation of **B** into **C** has been suggested[22b] to occur as shown in **Scheme IIA.1.2.** The protonation and dimerization of the ester **B** leads to the dimer **H**. Which on electron transfer, disproportionates to the manganese(IV) ester **I** and the manganese(VI) ester **C**. A species corresponding to **I** has apparently been observed by several groups of workers[20,26,27] and found to undergo oxidation to **C** in the presence of an excess of permanganate.[20]

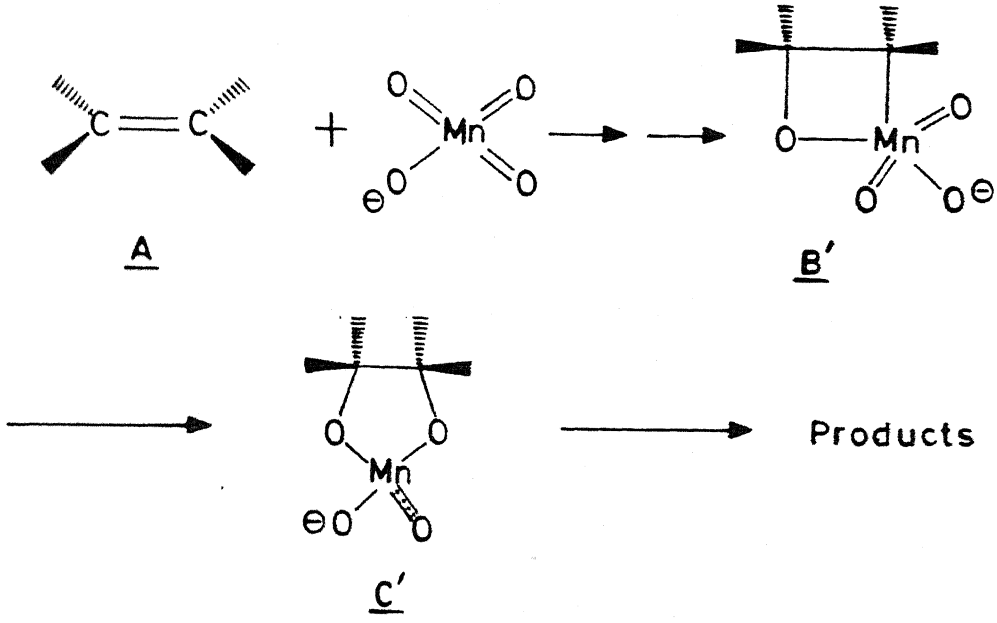
The mechanism of alkene oxidation by permanganate shown in **Scheme IIA.1.1** involving direct attack of the organic reductant on the metal-oxo bond represents a classical view. The modern ideas on alkene oxidation by metal oxides such as Cr(VI) oxide, Mo(VI) oxide, MnO_4^- or OsO_4 and RuO_4 have been advanced by Sharpless and coworkers[27a] and recently by Rappe and Goddard[27b] in their comprehensive mechanistic study using *ab initio* theoretical methods.

In the oxidation of alkene by $KMnO_4$, the novel aspect of Sharpless proposal[27a] involves the initial formation of a metallocyclooxetane intermediate (a σ-metal complex) *via* [2+2]

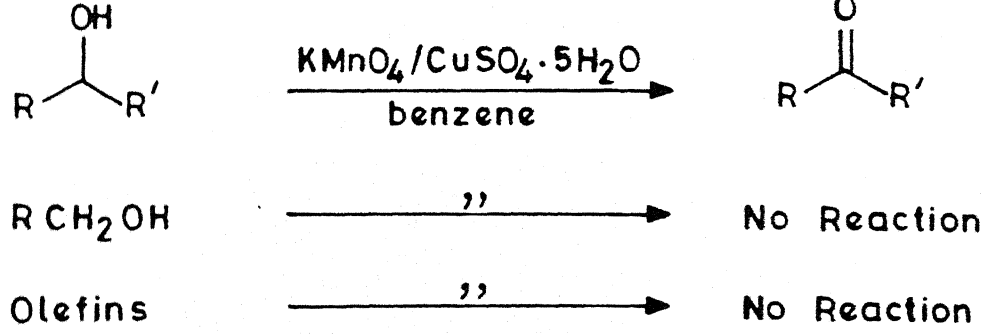
Scheme IIA-1.2



Scheme IIA-1.3



Scheme IIA-1.4



insertion of the alkene π-bond into a metal-oxo bond of manganese. This mechanistic approach rules out the direct [4+2] cycloaddition[4,28] as generally proposed for the carbon-carbon double bond oxidation by permanganate ion as shown for the intermediate **B** (**Scheme IIA.1.1**). Thus, in the oxidation of alkene **A** by MnO_4^- starting from the initial metallocyclooxetane intermediate **B'**, the reaction proceeds with an oxo-double bond, leading to conversion of a spectator oxo into an oxo-triple bond, thus driving the formation of the cyclic manganate(V) diester **C'** via rearrangement of **B'**. Formation of **C'** (a π-metal complex) is thus expected to be enhanced by simultaneous formation of triple-bonded spectator oxo group, that forms when two d-orbitals are available for bonding to a single oxygen;[27b] the ester **C'** then breaks to products **(Scheme IIA.1.3)**. It is noteworthy that in the oxidation of alkenes with potassium permanganate, the diol products are dominant without significant epoxide formation.[2-4,6] These findings are also supported by the theoretical studies.[27b]

Permanganate Oxidation Under Heterogeneous Conditions
Oxidation by Permanganate-coated Solid Supports

The classical oxidation of alcohols with permanganate has now been supplemented by a new technique involving solid supports. The use of inorganic and polymer supports as alternatives to organic solvents has already found wide application in organic and inorganic chemistry, biochemistry and biology.[29] It has been found that a large number of substitution, elimination, addition, oxidation and reduction reactions can be

achieved by use of insoluble or polymer supported reagents.[30] The use of heterogeneous reagents often increases the ease of execution and the selectivity of specific synthetic procedures.[29b,30] This is particularly true for oxidation reactions where the use of solid oxidants gives products that are not contaminated with reduced oxidant as frequently encountered, when the reaction is carried out in aqueous solutions[2,3] or in organic solvents with the aid of phase transfer agents.[14,28a]

Recent publications have described the heterogeneous oxidation of organic compounds by chromyl chloride chemisorbed on silica/alumina,[30b] pyridinium chlorochromate or dichromate on molecular sieves,[30c] chromium trioxide on graphite, Celite or silica gel,[30d] alumina or silica supported sodium metaperiodide,[30e] clay supported iron(III) nitrate,[30f] silver carbonate on Celite,[30g] and polymer supported iodate, periodate, pyridinium dichromate or hypochlorite.[30h]

Although chromium(VI),[31] iron(III),[32] periodate[33] and hypochlorite[34] have also been used as solid oxidants, the largest number of synthetic applications have come from the use of permanganate in contact with molecular sieves,[35] silica gel,[35,36] alumina,[37] or metal cations such as sodium(I)-monohydrate[38] or copper(II)-pentahydrate.[39]

Regen and Koteel[35] discovered that $KMnO_4$ can be activated by the simple process of impregnation on molecular sieves, silica gel or certain clays; the reagent can be used for the oxidation of alcohols in benzene.

Potassium permanganate supported on silica gel has been used for the conversion of γ-nitro ketones into the corresponding 1,4-diketones,[40] and also for the carbon-carbon double bond cleavage.[41] Zinc permanganate supported on silica gel has been reported[42] to perform the following transformations: acetylene to α-diketone and cyclic olefin to ketol.

Recently, Menger and Lee[39a] found that $CuSO_4.5H_2O$ [although by itself is inert toward alcohols] activates the oxidizing ability of powdered $KMnO_4$. Using $KMnO_4$ and $CuSO_4.5H_2O$, it is possible to convert secondary alcohols into ketones rapidly in high yields under very mild conditions, while primary alcohols are oxidized only slowly.[39a] Apparently, one function of the copper salt is to supply water in traces. Drying of the mixed solid reagent over P_2O_5 lowered the formation of carbonyl compounds.[39a] Surprisingly, although aqueous permanganate reacts almost instantaneously with carbon-carbon double bonds in solution,[4,20-22] olefins are inert towards $KMnO_4$ supported on $CuSO_4.5H_2O$[39] (**Scheme IIA.1.4**).

Many other organic compounds such as arenes, alkynes, amides and oxiranes which are oxidized by permanganate in solution, show little or no reactivity towards solid permanganate salts.[39] Only alcohols,[2] sulfides,[3] and aldehydes[43] are easily oxidized both, under homogeneous and heterogeneous conditions.[39]

The mechanism of the heterogeneous oxidation of saturated secondary and β,γ-unsaturated alcohols by $KMnO_4/CuSO_4.5H_2O$ has recently been discussed in detail.[44] Although secondary

alcohols undergo a rapid oxidation with $KMnO_4/CuSO_4.5H_2O$, presence of an alkene completely inhibits this reaction, apparently by formation of π-complexes on the surface of the oxidant.[44] When mixtures of saturated secondary and β,γ-unsaturated alcohols are treated with hydrated copper permanganate, the unsaturated alcohols are preferentially oxidized. Although the converse is true when each alcohol is oxidized separately. When these results are taken together with the previous observations which indicate that carbon-carbon double bonds bind to the reactive sites on copper permanganate. It seems likely that the unsaturated alcohol is first attached to the oxidant by a bond and subsequently oxidized.[44] Non-allylic unsaturated alcohols are not oxidized under the conditions, whereas allylic alcohols lead to carbonyl compounds in good yields[39]

Recently, $KMnO_4$ supported on $CuSO_4.5H_2O$ and in the presence of KOH has been used for the oxidation of primary alcohols to acids and diols to lactones in high yields.[45] $KMnO_4$ impregnated on $CuSO_4.5H_2O$ has been found to be an useful reagent for the oxidation of β-hydroxy nitrosamines to β-ketonitrosamines.[46]

Direct Oxidation of Alkenes to α-Diketones

Since α-diketones are valued as precursors of transition metal ligands, of acetylenes, and of heterocyclic compounds, the direct conversion of alkenes to α-diketones constitutes an important methodology in organic synthesis. Sharpless and coworkers[47] have found that the oxidation of symmetrically

disubstituted alkenes with potassium permanganate in cold acetic anhydride provides ready access to rather rare, α-diketone functional group (**Scheme IIA.1.5**).

Although this procedure[47] is now the method of choice for preparing α-diketones directly from acyclic or large-ring alkenes, it fails to produce significant amounts of α-diketones from smaller-ring alkenes and it involves tedious work-up procedure.

IIA.2 RESULTS AND DISCUSSION

Oxidation of Alkenes Under Heterogeneous Conditions

Although alkenes are found to be inert towards potassium permanganate supported on $CuSO_4.5H_2O$ and retard the reaction by forming a π-complex with the permanganate ion,[44] we observed that a slight modification of the heterogeneous permanganate oxidation with $KMnO_4/CuSO_4.5H_2O$ can be used effectively for the direct conversion of olefins to α-diketones/α-hydroxy ketones under very mild conditions. It turns out that when olefins are treated with a well ground mixture of $KMnO_4/CuSO_4.5H_2O$ in dichloromethane containing catalytic amounts of tert.butyl alcohol/water at room temperature, α-diketones/α-hydroxy ketones are obtained in good yields. The results obtained by this modified procedure are summarized in **Table IIA.2.1.**

There are a number of interesting features of this methodology which are worth pointing out. The most common method widely used for the conversion of olefins to α-diketones is that

Scheme-IIA-1.5

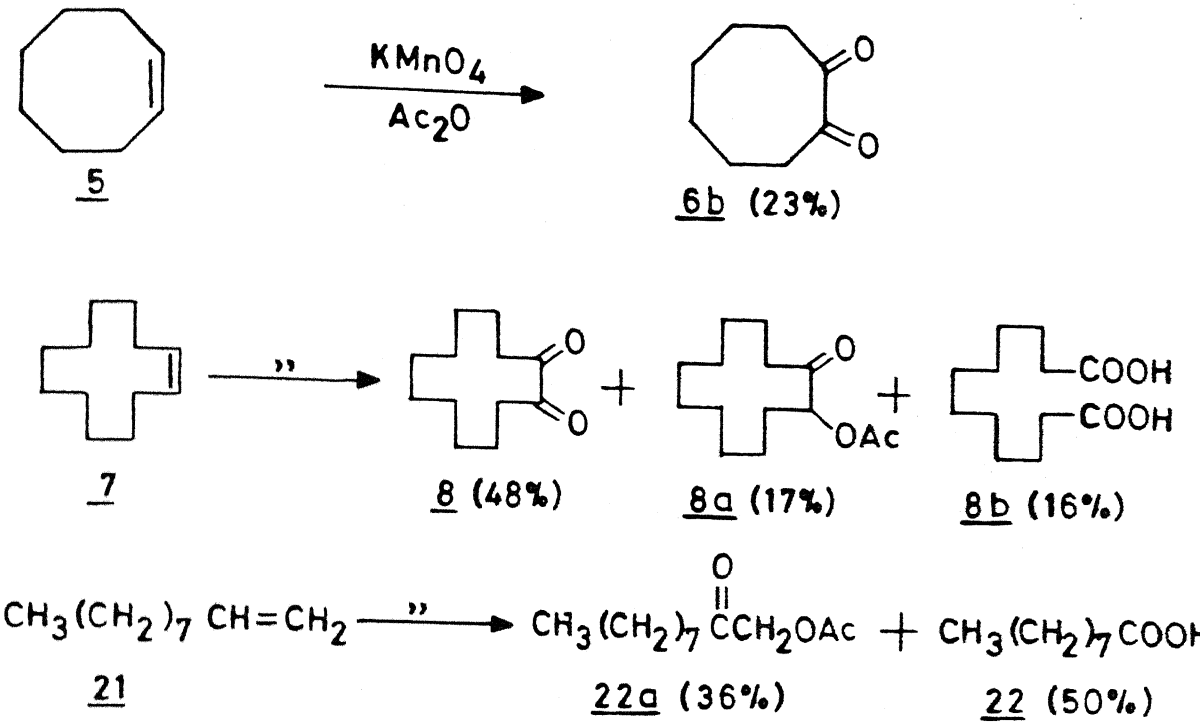


Fig.IIA-2.1

Formation of a Omega-phase

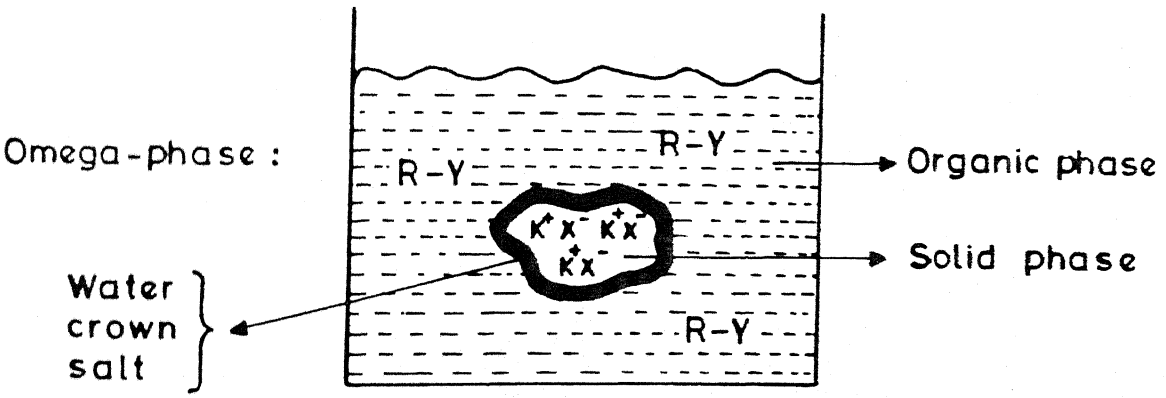
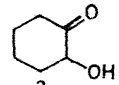
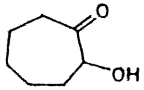
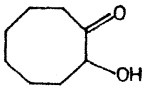
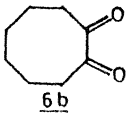
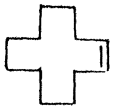
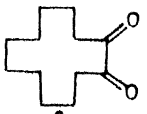
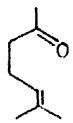
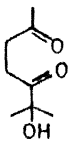
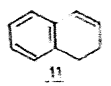
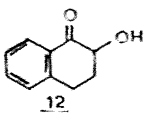
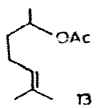
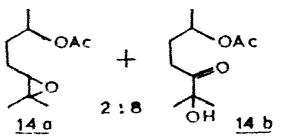
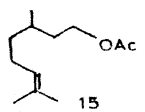
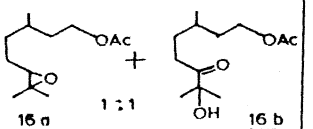
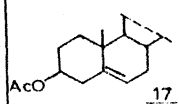
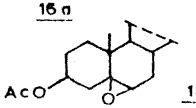
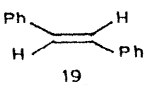
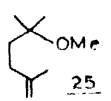
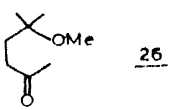
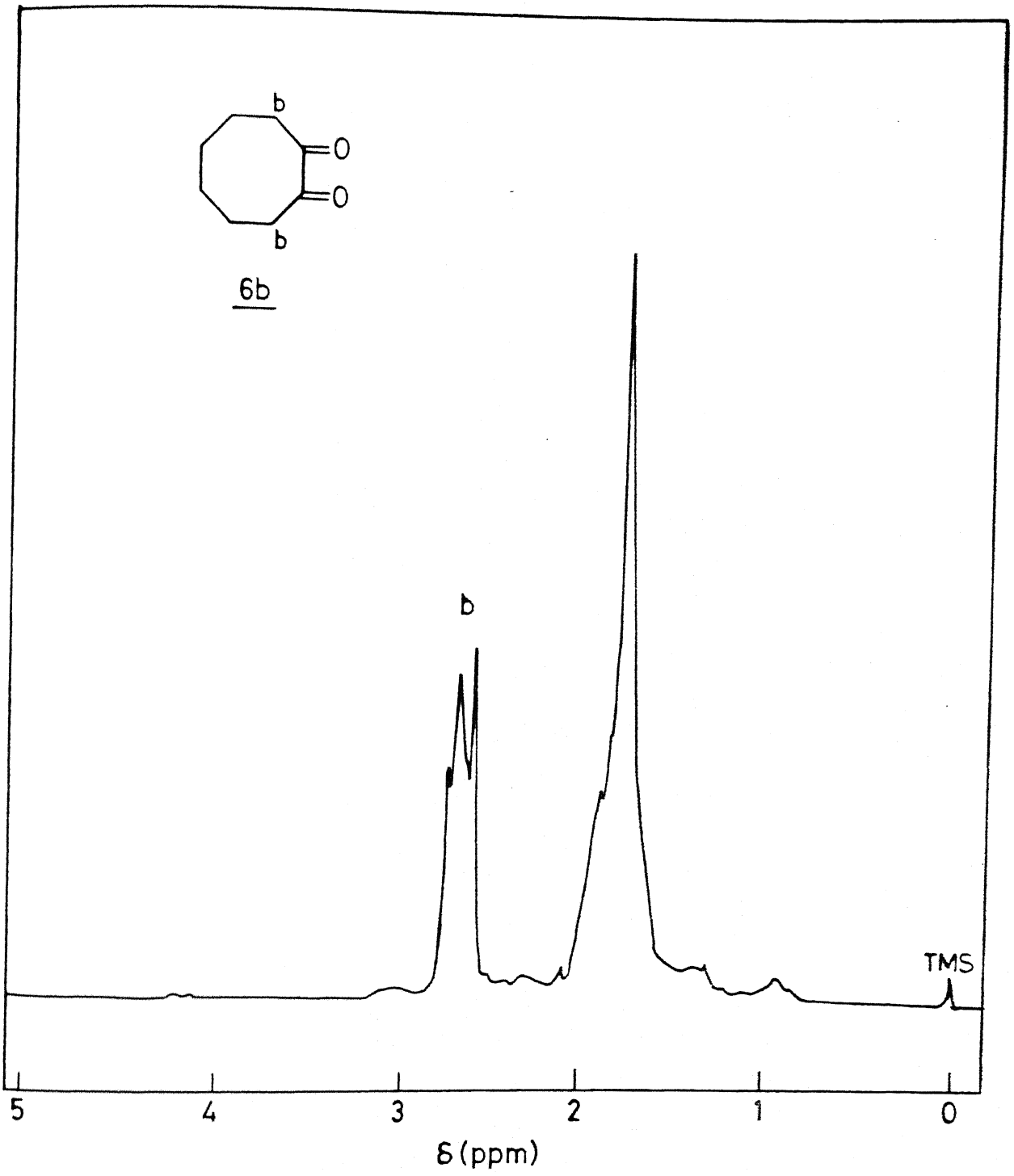


Table IIA 2.1 OXIDATION OF OLEFINS WITH $KMnO_4$ / $CuSO_4 \cdot 5H_2O$ AT 25°C

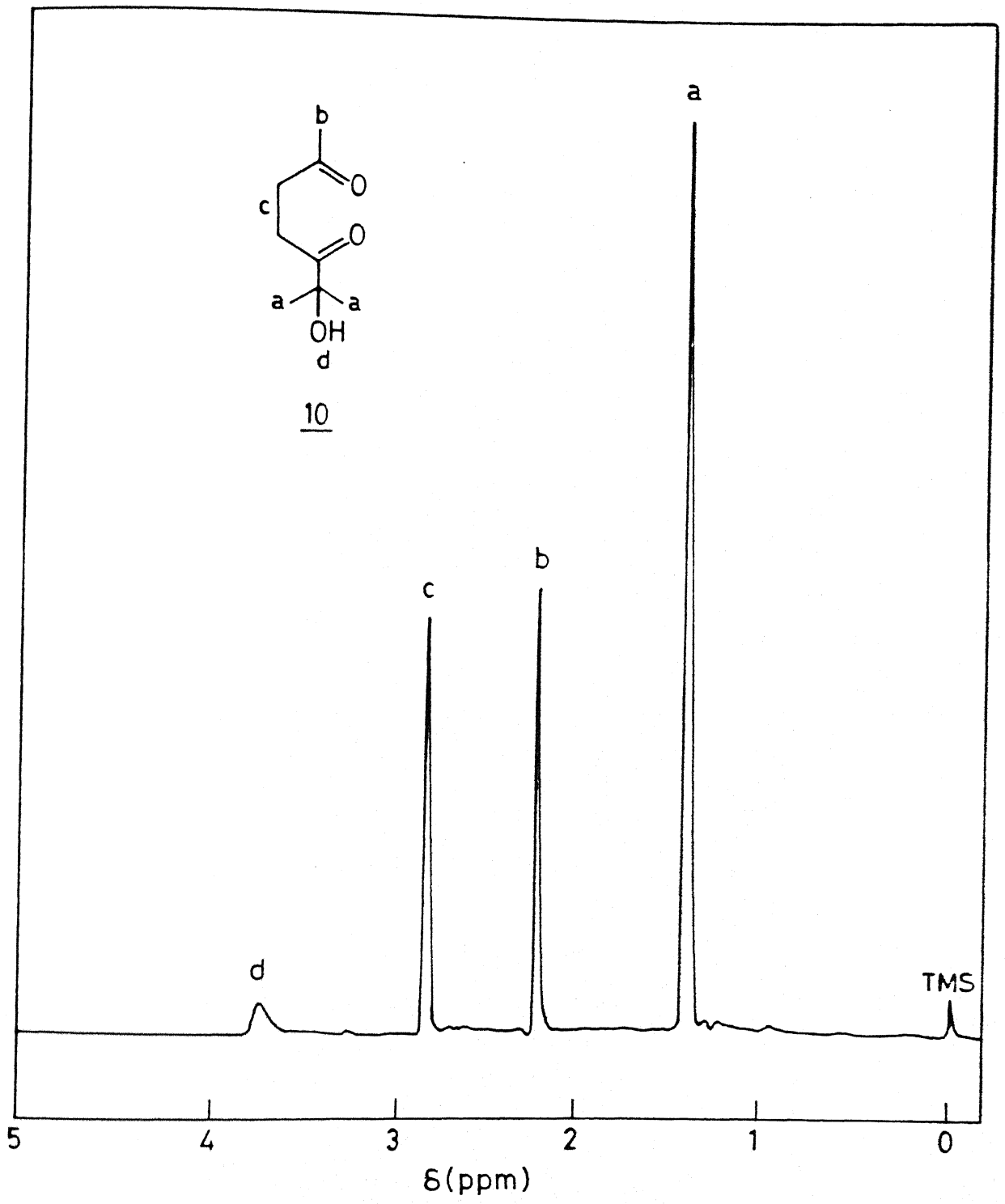
ENTRY	SUBSTRATE	m mol	OXIDANT $KMnO_4$: $CuSO_4 \cdot 5H_2O$: $Cu(OAc)_2 \cdot H_2O$ in gm	t BuOH : H_2O ml	PRODUCT	REACTION TIME h	YIELD %
1	 1	4	4 : 2 : 0	1 : 0.2	 2	0.5	30
2	 3	4	4 : 2 : 0	1 : 0.2	 4	0.5	59
3	 5	4	4 : 2 : 0	1 : 0.2	 6a	0.5	50
4	5	2	4 : 2 : 0	1 : 0.3	 6b	4	48
5	 7	2	4 : 2 : 1	1 : 0.3	 8	6	58
6	 9	4	4 : 2 : 0	1 : 0.3	 10	2	79

Contd...

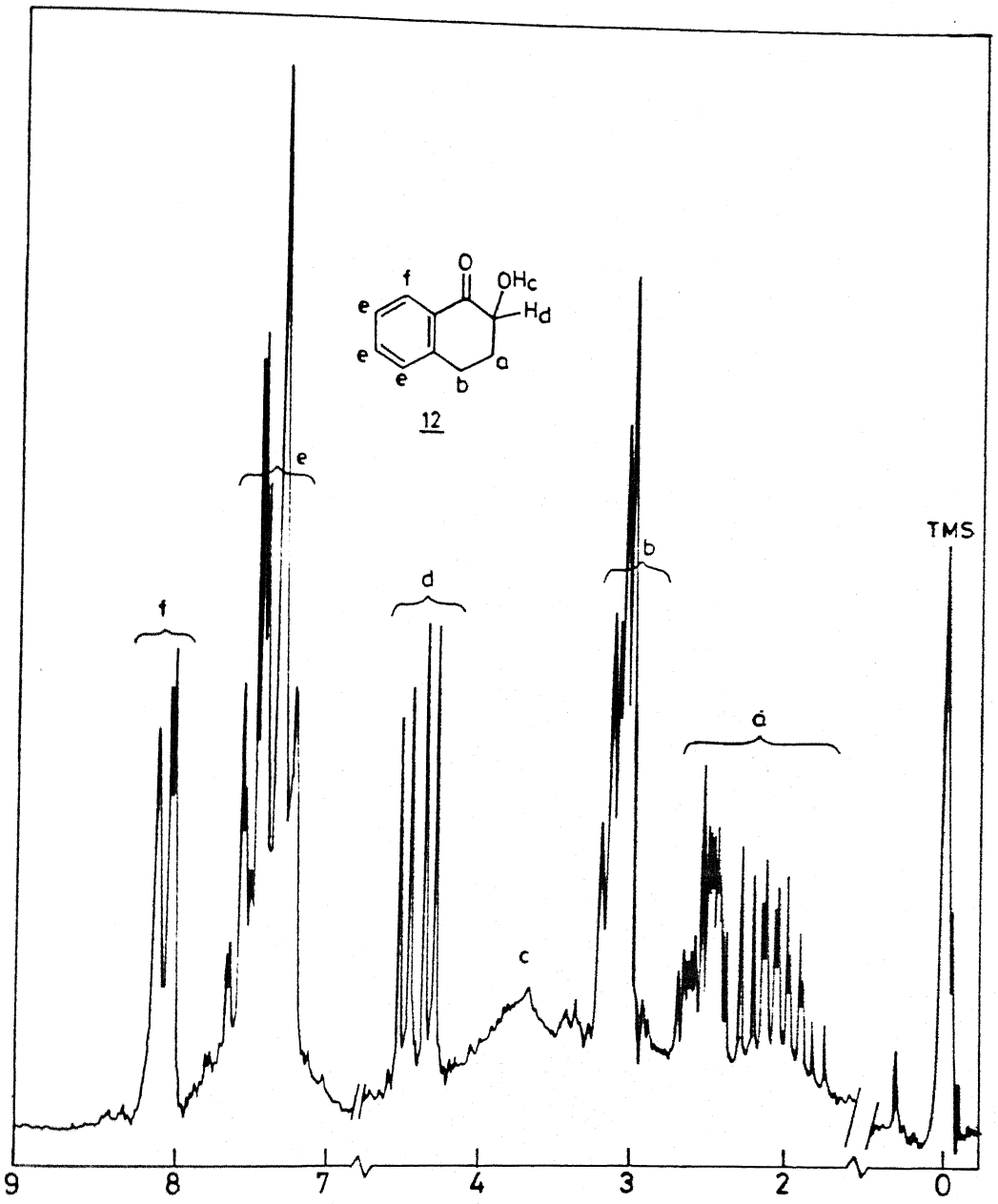
7	 11	2	4 : 2 : 0	1 : 0.2	 12	3	55
8	 13	4	4 : 2 : 0	1 : 0.3	 14 a : 14 b = 2 : 8	2.5	78
9	 15	4	4 : 2 : 0	1 : 0.3	 16 a : 16 b = 1 : 1	2	80
10	 17	2	4 : 2 : 0	1 : 0.4	 18	2	92
11	 19	4	4 : 2 : 0	1 : 0.4	Ph – CHO 20	2	92
12	$CH_3(CH_2)_7CH=CH_2$ 21	4	4 : 2 : 0	1 : 0.3	$CH_3(CH_2)_7COOH$ 22	4	72
13	$CH_3(CH_2)_4CH=CH-CH_3$ 23	4	4 : 2 : 0	1 : 0.3	$CH_3(CH_2)_4COOH$ 24	4	78
14	 25	4	4 : 2 : 0	1 : 0.3	 26	4	62
15	Ph – C ≡ C – Ph 27	2	4 : 2 : 0	1 : 0.3	Ph – C(=O) – C(=O) – Ph 28	24	97



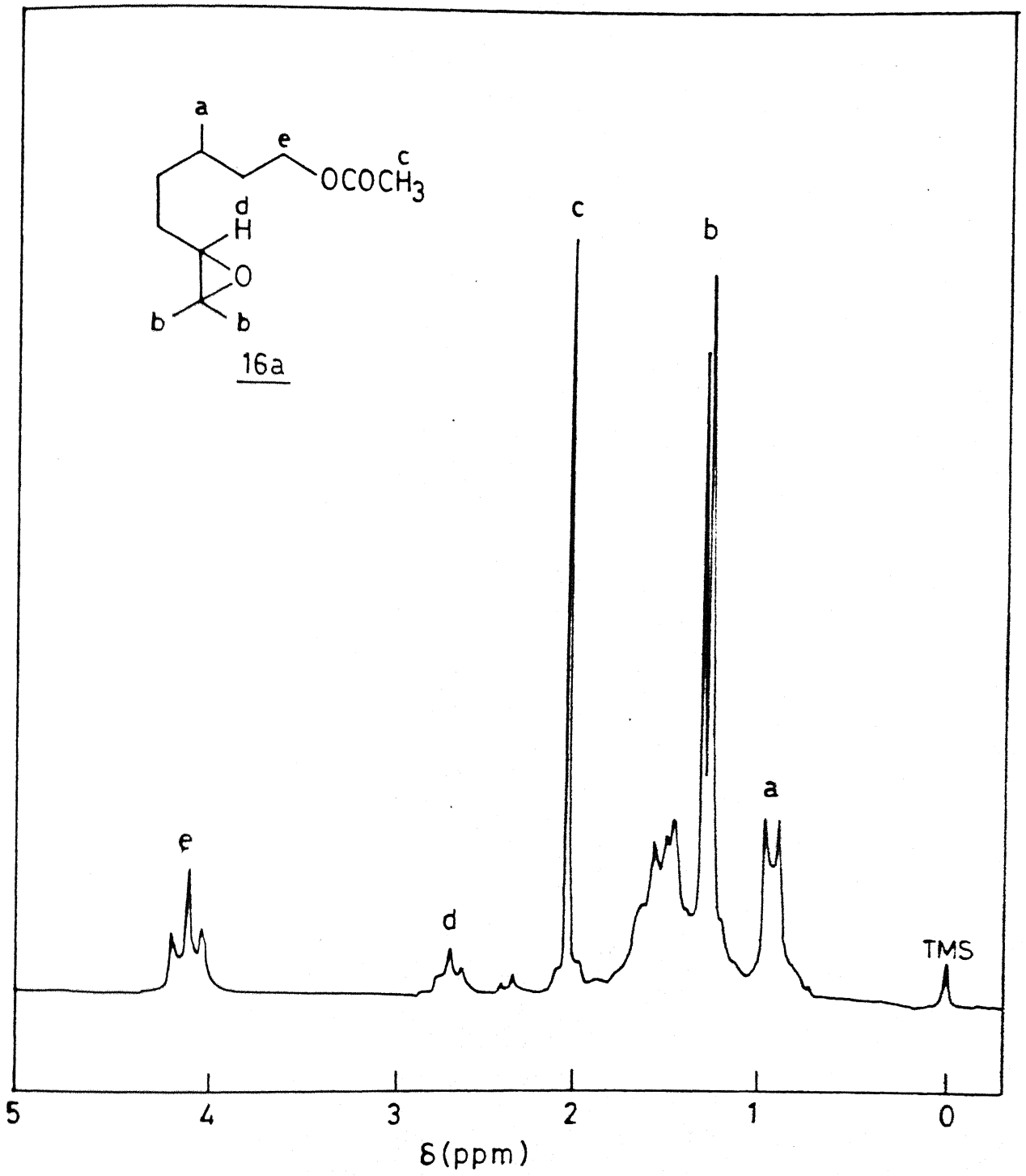
^{1}H NMR Spectrum of (80 MHz) of 6b



^{1}H NMR Spectrum (80 MHz) of 10



^{1}H NMR spectrum (80 MHz) of 12



^{1}H NMR Spectrum (80 MHz) of 16a

of Sharpless[47] using $KMnO_4$-acetic anhydride system which involves a tedious work-up procedure and fails to produce significant amounts of α-diketones from small-ring olefins. cis-Cyclooctene the smallest cyclic olefin to be successfully oxidized, gave only a 23% yield of diketone.

On the other hand the present methodology gave the α-hydroxy ketones **2** (30%), **4** (59%) and **6a** (50%) from the corresponding olefins. In the case of cyclooctene **5** when the same reaction was done along with cupric acetate (1 mole equiv.) for 4 h, the intermediate α-hydroxy ketone **6a** was converted to cyclooctane 1,2-dione **6b** (48%). Cyclododecene **7** under similar conditions gave 1,2-dione **8** (58%). Oxidation of olefinic ketone **9** afforded the hydroxy ketone **10** in 79% yield. In the reaction of tetrahydronaphthalene **11** β-hydroxy-α-tetralone **12** was obtained in 55% yield.

Olefinic substrates **13**, **15** and **17**, however, showed some interesting pattern of reactivity. In the case of oxidation of **13** with $KMnO_4/CuSO_4.5H_2O$ in the presence of catalytic amount of water and tert.butanol, epoxide **14a** and hydroxy ketone **14b** (2:8) were obtained in 78% yield. Under similar conditons, citronellol acetate **15** gave a (1:1) mixture of epoxide **16a** and hydroxy ketone **16b** (80%) and cholesteryl acetate **17** afforded the β-epoxide **18** as the only product (92%). It is noteworthy that in general, the oxidation of alkenes with potassium permanganate under aqueous conditions, yields insignificant amount of epoxides.[4,6,27b] However, in the present study the epoxides **14a**, **16a** and **18** were found to be formed either as one of the

products or sole product in the reaction of substrates **13**, **15** and **17** respectively. It is obvious that the epoxide formation increases with increasing lipophilicity of the substrates. This interesting observation can be exploited for the synthesis of epoxides from suitable olefinic precursors using permanganate ion.

trans-Stilbene **19** and acyclic olefins **21**, **23** and **25** underwent oxidative cleavage under the above reaction conditions. However, diphenyl acetylene **27** yielded benzil **28** in high yield (97%). This reaction would be particularly useful for cyclic (small, medium and large) olefins and acylic trisubstituted olefins.

Omega Phase Catalysis

In studying the kinetics of substitution of benzyl halides with cyanide ion catalyzed by 18 crown-6, Liotta[48] observed a dramatic increase in rate with the addition of minute quantities of water.[49] Under these conditions, the catalyst is no longer present in the organic phase, but is located on the surface of the solid salt particles. It is conjectured that the initial water added to the system coats the surface of the solid salt phase. It is believed that it is this aqueous salt coating which extracts the 18 crown-6 from the organic phase onto the surface. This is pictorially represented in **Figure IIA.2.1** and this new region i.e. omega phase is intimately involved in the catalytic reaction process. A non-classical phase transfer system i.e., omega phase catalysis has been invoked to explain the role of water[49] in these reactions. It is very likely that

in this oxidation, the water/tert.butyl alcohol forms a third phase, i.e., omega phase by surrounding the inorganic solids and it is in or on or by means of this interface that the reaction takes place. It is believed that the tert.butyl alcohol acts as a catalyst. The amount of tert.butyl alcohol and water added in this reaction is very crucial for the success of this reaction. In the absence of either water or tert.butyl alcohol, the reaction does not take place. Unusual formation of epoxides would be in line with omega phase catalysis. This observation is very interesting and needs to be explored further.

Omega phase formation has been found to occur with a variety of catalysts and salts.[48] Indeed, initial experiments have demonstrated that triglyme and tetraglyme are extracted from the organic phase (toluene or benzene) on to the surface of inorganic salts upon addition of small amount of water. Similarly, a range of alkali and alkaline earth metal salts including KSCN, KF, CH_3COOK, LiI, NaBr, $MgCl_2$ and $CaCl_2$ have been shown to participate in omega phase formation.

Compared to all the existing procedures for the direct oxidation of olefins to α-diketones this method appears to be more general, the reaction conditions are milder and the yields of the product are usually better. Our modified permanganate oxidation makes this relatively rare functional group more readily accessible.

IIA.3 EXPERIMENTAL

General Procedure

As described in Chapter IA.

Materials

$KMnO_4$ (E. Merck), $CuSO_4.5H_2O$ (E. Merck) and $Cu(OAc)_2.H_2O$ (E. Merck) were used as such. Commercial grade solvents were distilled prior to use. Dichloromethane was distilled over P_2O_5. Cholesteryl acetate, citronellol acetate were prepared by known methods.

Chromatography

As described in Chapter IA.

Physical Data

As described in Chapter IA.

Oxidation of Cyclohexene 1

A mixture of solid $KMnO_4$ (4.0 g) and $CuSO_4.5H_2O$ (2.0 g) was ground to a fine powder in a pestle and mortar. To this water (200 µL) was added and the slightly wet mixture was transfered to a reaction flask. To a stirred suspension of this mixture in dichloromethane (15 mL) was added cyclohexene 1 (0.329 g, 4 mmol) in dichloromethane (5 mL) followed by the addition of tert.butanol (1.0 mL). Within a few minutes the reaction mixture started to reflux for a while (5 min) and then cooled down. After stirring the reaction mixture for 0.5 h at room temperature (25 ^oC) it was filtered over a pad of Celite and

6b[53] (0.134 g, 48%) was obtained after distillation, b.p. 130 °C/3 mm (lit.[54] b.p. 130 °C/3 mm).

IR (thin film) : 1702 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.7 (s, 8 H), 2.53-2.76 (m, 4 H).

Oxidation of Cyclododecene 7

Cyclododecene **7** (0.332 g, 2 mmol) under similar reaction conditions afforded cyclododecane 1,2-dione **8** (0.227 g, 58%) after distillation, b.p. 82-85 °C/0.1 mm, as a yellow solid, m.p. 42-44 °C (lit.[55] m.p. 43 °C).

IR (thin film) : 1701 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.3 (s, 16 H), 2.66-2.86 (m, 4 H).

Oxidation of Compound 9

When a mixture of $KMnO_4$ (4.0 g), $CuSO_4.5H_2O$ (2.0 g) and water (300 μL) in dichloromethane (15 mL) was treated with compound **9** (0.568 g, 4 mmol) in dichloromthane (5 mL) and tert.-butanol (1 mL), yielded, after chromatography, compound **10** (0.550 g, 79%).

IR (thin film) : 3450, 1720, 1705 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.43 (s, 6 H), 2.2 (s, 3 H), 2.83 (s, 4 H), 3.76 (br s, 1 H).

MS (m/e) : 159 ($M^+ + 1$).

Anal. Calcd for $C_8H_{14}O_3$: C, 60.76; H, 8.86.

Found: C, 60.88; H, 8.94.

Oxidation of 1,2-Dihydronaphthalene 11

When a mixture of $KMnO_4$ (4.0 g), $CuSO_4.5H_2O$ (2.0 g) and

water (200 μL) in dichloromethane (15 mL) was treated as above, with compound **11** (0.260 g, 2 mmol) in dichloromethane (5 mL) and tert.butanol (1 mL), 2-hydroxy-1-tetralone **12** (0.178 g, 55%), m.p. 36-37 °C (lit.[56] 36-36.5 °C), was obtained after chromatography on silica gel.

IR (thin film) : 3460, 3060, 1680, 1600 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.76-2.73 (br m, 2 H), 3.06-3.26 (m, 2 H), 3.8 (br s, 1 H), 4.26-4.56 (dd, 1 H), 7.26-7.66 (m, 3 H), 8.0-8.23 (m, 1 H).

Oxidation of Compound 13

When a mixture of $KMnO_4$ (4.0 g), $CuSO_4.5H_2O$ (2.0 g) and water (300 μL) in dichloromethane (15 mL) was treated with compound **13** (0.680 g, 4 mmol) in dichloromethane (5 mL) and tert.butylalcohol (1 mL), epoxy acetate **14a** (0.119 g, 16%) and ketol **14b** (0.5 g, 62%) were obtained after chromatographic purification on silica gel (1:10, ether-petroleum ether).

Compound 14a

IR (neat) : 1735 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.20-1.30 (3s, 9 H), 1.52-1.76 (m, 4 H), 2.04 (s, 3 H), 2.64-2.76 (t, 1 H), 4.80-5.04 (m, 1 H).

MS (m/e) : 187 ($M^+ + 1$), 127, 109, 85, 43.

Compound 14b

IR (neat) : 3460, 1735, 1720 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.0-1.06 (d, 3 H), 1.36 (s, 6 H), 1.80-1.96 (m, 2 H), 2.04 (s, 3 H), 2.52-2.61 (d, 2 H),

3.32 (br,s, 1 H), 4.72-5.06 (m, 1 H).

MS (m/e) : 203 ($M^+ + 1$), 143, 125, 59, 43.

Oxidation of Citronellol acetate 15

To a mixture of $KMnO_4$ (4.0 g), $CuSO_4.5H_2O$ (2.0 g) and water (300 µL) in dichloromethane (15 mL) was added citronellol acetate **15** (0.792, 4 mmol) in dichloromethane (5 mL) and tert.butanol (1 mL) and stirred for 2 h. On purification by chromatography the epoxy compound **16a** (0.342 g, 40%)

IR (thin film) : 1735 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 0.93 (d, 3 H), 1.33 (d, 6 H), 1.43-1.83 (m, 7 H), 2.06 (s, 3 H), 2.66-2.83 (t, 1 H), 4.0-4.3 (t, 2 H).

MS (m/e) : 194 (M^+)

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.29; H, 10.28.

Found: C, 67.38; H, 10.35.

and ketol-acetate **16b** (0.368 g, 40%) were obtained.

IR (thin film) : 3450, 1735, 1710 cm^{-1}.

^1H NMR($CDCl_3$) : δ 0.9 (d, 3 H), 1.34 (s, 6 H), 1.43-1.83 (m, 5 H), 2.0 (s, 3 H), 2.40-2.56 (t, 2 H), 3.7 (br s, 1 H), 4.0-4.2 (t, 2 H).

MS (m/e) : 231 ($M^+ + 1$).

Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.61; H, 9.56.

Found: C, 62,82; H, 9.68.

Oxidation of Cholesteryl acetate 17

Cholesteryl acetate **17** (0.857 g, 2 mmol) was treated

under similar conditions with $KMnO_4$ (4.0 g), $CuSO_4.5H_2O$ (2.0 g) water (400 µL) and tert.butanol (1 mL), to give β-epoxy compound **18** (0.820 g, 92%), m.p. 110-112 °C (lit.[57] m.p. 111-112 °C).

Oxidation of trans-Stilbene 19

trans-Stilbene **19** (0.720 g, 4 mmol) was allowed to react with a mixture of $KMnO_4$ (4.0 g), $CuSO_4.5H_2O$ (2.0 g), water (300 µL) and tert.butanol (1 mL), to give benzaldehyde **20** (0.780 g, 92%), found to be identical with an authentic sample.

Oxidation of 1-Decene 21

A mixture of $KMnO_4$ (4.0 g), $CuSO_4.5H_2O$ (2.0 g) and water (300 µL) was treated under similar conditions with 1-decene **21** (0.560 g, 4 mmol) and tert.butanol (1 mL), to yield nonanoic acid **22** (0.455 g, 72%), found to be identical with an authentic sample.

Oxidation of 2-Octene 23

When compound **23** (0.448 g, 4 mmol) was treated as above with $KMnO_4$ (4.0 g), $CuSO_4.5H_2O$ (2.0 g) water (300 µL) and tert.butanol (1.0 mL), hexanoic acid **24** (0.324 g, 78%) was obtained, found to be identical with an authentic sample.

Preparation of Compound 25

Sodium hydride (1.344 g of 50% dispersion in oil, 28 mmol) after washing for 2-3 times with dry petroleum ether was taken up in dry benzene (10 mL) under nitrogen atmosphere. 2,5-Dimethyl-hex-5-en-2-ol (1.024 g, 8 mmol) in dry benzene (5 mL)

was added to that slowly with stirring. After the addition was over, the mixture was stirred at room temperature for 1 h, then refluxed for 3 h, cooled to room temperature and methyl iodide (2.84 g, 20 mmol) in benzene (5 mL) was added. Then it was refluxed for 30 h, and cooled to room temperature. The reaction mixture was poured into water (30 mL) and extracted with ether. Combined ether extracts were washed once with water, brine and dried ($MgSO_4$). The organic layer was concentrated and the residue was purified by flash chromatography on silica gel (1:10, ether-petroleum ether) to yield **25** (0.580 g, 51%) as an oil.

IR (neat) : 3060, 1660 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.28 (s, 6 H), 1.37-1.81 (m, 2 H), 1.68 (s, 3 H), 2.03 (m, 2 H), 3.88 (s, 3 H), 4.63 (s, 2 H).

Oxidation of Compound 25

When a mixture of $KMnO_4$ (4.0 g), $CuSO_4.5H_2O$ (2.0 g) and water (300 µL) in dichloromethane (15 mL) was treated with compound **25** (0.568 g, 4 mmol) in dichloromethane (5 mL) and tert. butylalcohol (1 mL), keto-ether **26** (0.357 g, 62%) was obtained after chromatography purification on silica gel (1:10, ether-petroleum ether).

IR (neat) : 1715 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.28 (s, 6 H), 1.93 (m, 2 H), 2.12 (s, 3 H), 2.38 (m, 2 H), 3.87 (s, 3 H).

Anal. Calcd for $C_8H_{16}O_2$: C, 66.67; H, 11.11.

Found : C, 66.72; H, 11.14.

Oxidation of Diphenyl acetylene 27

Compound **27** (0.356 g, 2 mmol) was treated with a mixture of $KMnO_4$ (4.0 g), $CuSO_4.5H_2O$ (2.0 g), water (300 μL) and tert.butanol (1 mL), under similar conditions of oxidation to afford benzil **28** (0.407 g, 97%; m.p. 94-95 ^oC) as a yellow solid, found to be identical with an authentic sample.

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CHAPTER IIB

HETEROGENEOUS PERMANGANATE OXIDATION (OMEGA PHASE CATALYSIS) OF 1,5-DIENES: SYNTHESIS OF 5-SUBSTITUTED BUTANOLIDES

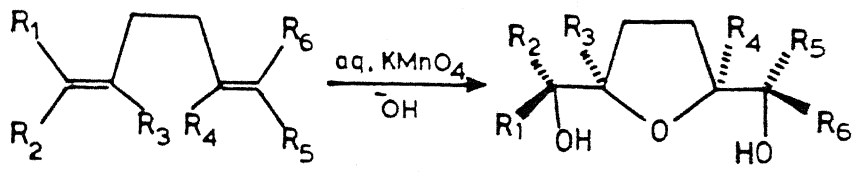
IIB.1 INTRODUCTION

Permanganate Oxidation of 1,5-Dienes Under Homogeneous Conditions

Construction of stereochemically unambiguous five- and six-membered cyclic ethers, common structural subunits in a wide variety of natural products,[1] has always been a challenge to the synthetic organic chemist. In 1965, Klein and Rojahn[2] reported that the oxidation of 1,5-dienes structurally related to geraniol and nerol with potassium permanganate under slightly alkaline conditions afforded 2,5-bis(hydroxymethyl)tetrahydrofurans with relative stereochemistry as shown in **Scheme IIB.1.1.**

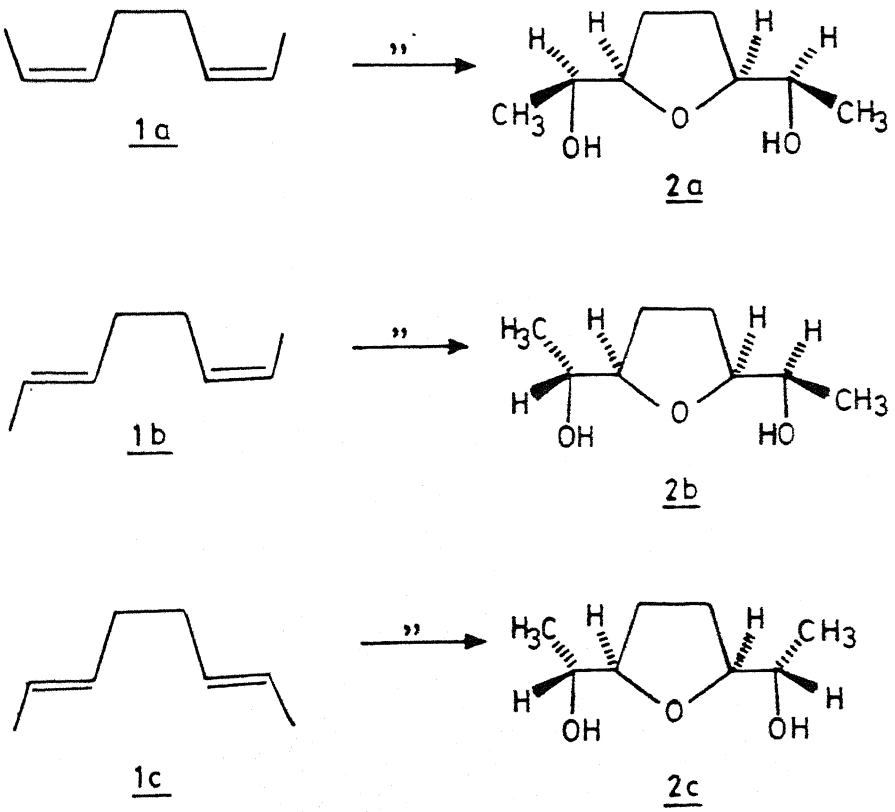
From the mechanistic point of view these results are provocative, particularly, in the light of the recent proposals of Sharpless concerning the mechanism of oxidation of olefins by oxo-transition metal species.[3] They are especially intriguing from the standpoint of synthetic chemistry in suggesting that stereocontrolled synthesis of 2,5-bis(hydroxymethyl)tetrahydrofuran with four chiral centers may be accomplished via stereoselective synthesis of appropriate 1,5-diene precursor.

Scheme-II B-1.1



1 2

Scheme-II B-1.2



1a 2a

1b 2b

1c 2c

As part of a study on the scope and mechanism of this reaction, Walba[4] described the oxidation of three isomeric 2,6-octadienes **1a-c** with aqueous potassium permanganate to yield diols **2a-c**, respectively with more than 97% stereospecificity **(Scheme IIB.1.2)**.

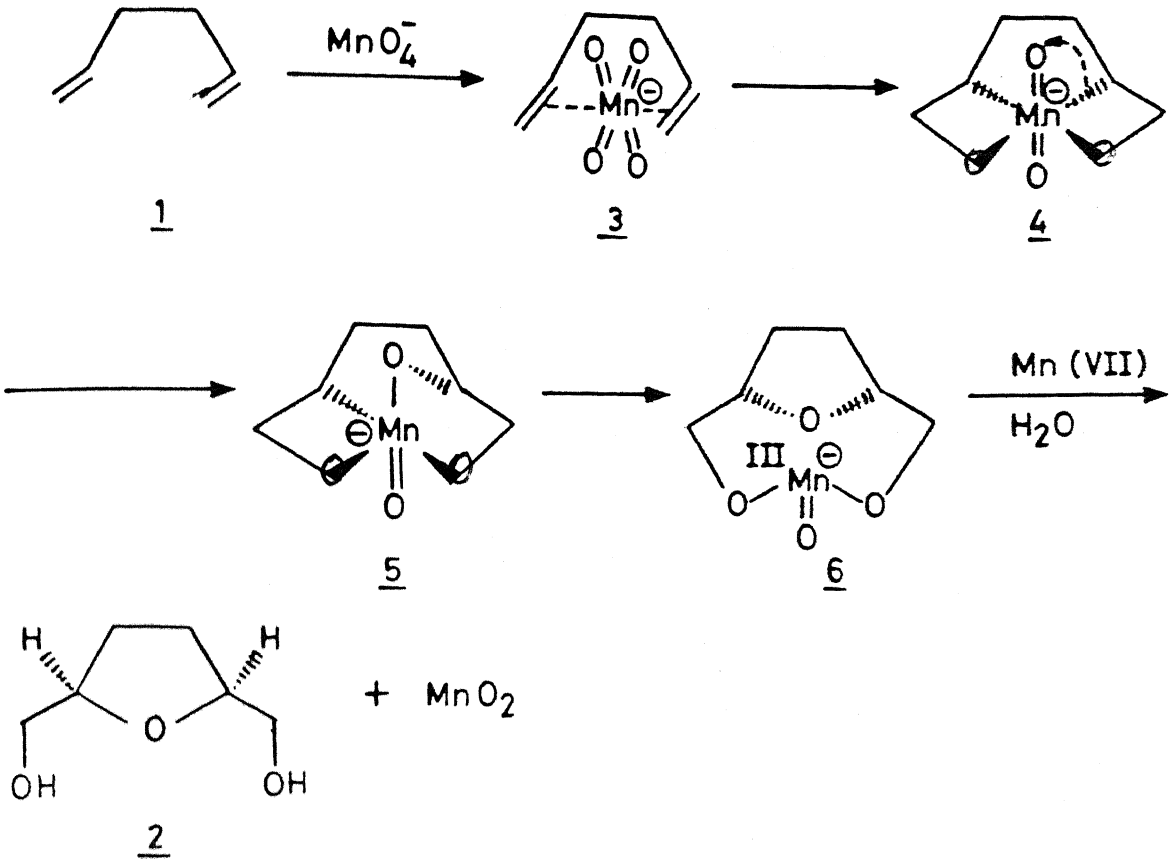
By invoking Sharpless proposals,[3] Walba evinced the formation of the high stereoselectivity and retention of configuration in this reaction **(Scheme IIB.1.3)**.[4] Initial formation of the bis-π-complex 3 between diene and MnO_4^- is followed by two Sharpless type [2+2]-additions giving the remarkably unstrained octahedral Mn(VII) intermediate **4**. Alkyl migration gives **5** with retention of configuration which is followed by the key reductive elimination to afford Mn(III) diester **6** with retention of configuration. Oxidation of intermediate **6** and hydrolysis then yields MnO_2 and diol **2** with correct relative stereochemistry.

Similar results were obtained by Baldwin[5] in the oxidation of labeled 1,5-hexadienes with alkaline potassium permanganate.

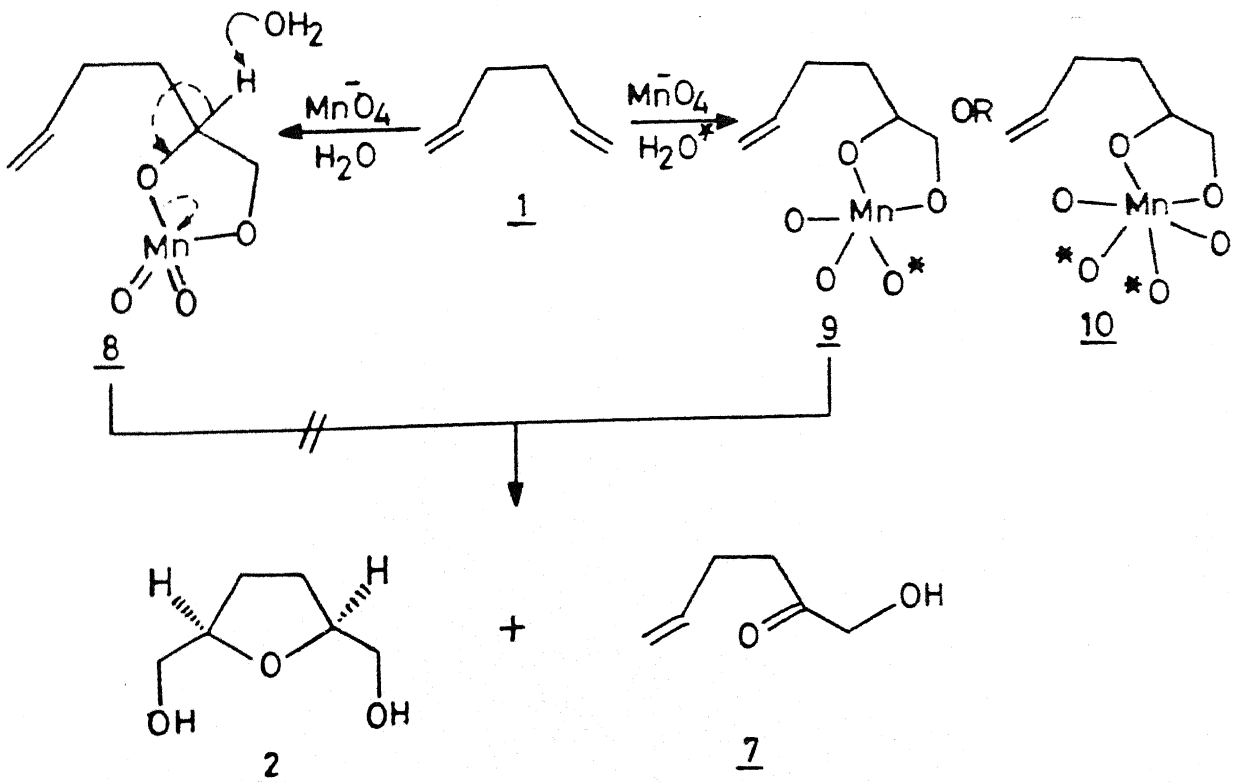
Recent ^{18}O-labeling experiments provided indirect evidence for the presence of transient penta- and hexacoordinated species during permanganate oxidation of 1,5-hexadiene **1** to give the tetrahydrofuran diol **2** and the ketol **7** **(Scheme IIB.1.4)**.[6]

Wolfe's findings[6] are incompatible with the mechanism proposed by Klein and Rojahn[2] and by Walba and coworkers[4] for the oxidation of 1,5-hexadiene **1**, in which all the three oxygen atoms of the product are derived from a single molecule

Scheme-IIB-1.3



Scheme-IIB-1.4



of permanganate *via* a 1:1 diene-permanganate complex. Wolfe favored a sequential oxidation[7] of the two double bonds *via* the manganese(VI) ester **8**. It must be concluded[7] that the solvent is incorporated to carbon *via* the manganese atom i.e., the pentacoordinated species **9** or the hexacoordinated species **10** transfers a labeled oxygen atom and another oxygen atom to the second double bond. Thus, the experimental result is consistent with the conclusion[6] that oxidation of the second double bond by a hexacoordinated manganate(VI) ester **10** would lead to the diol **2**, in which two oxygen atoms are derived from the permanganate and one from the solvent **(Scheme IIB.1.4)**.

IIB.2 RESULTS AND DISCUSSION

Potassium permanganate impregnated on $CuSO_4.5H_2O$ and in the presence of catalytic amount of water and *tert*.butyl alcohol has been found to be an excellent reagent system for the direct conversion of olefins to α-diketones and α-hydroxy ketones under very mild conditions possibly involving omega phase catalysis **(Chapter IIA)**. In order to explore further the synthetic utility of heterogeneous permanganate oxidation under conditions of omega phase catalysis, we chose to study the behaviour of a few 1,5-dienes. The objective at that stage was to find out whether in fact the 1,5-dienes would take a similar course like aqueous alkaline permanganate oxidations reported earlier[2,4-6] and if so whether we would be able to improve upon that useful methodology.

Under the aqueous conditions, $KMnO_4$ oxidation of 1,5-hexadienes is known to give 2,5-bis(hydroxymethyl)tetrahydrofurans with high degree of stereospecificity.[2,4-6] Surprisingly, heterogeneous permanganate oxidation of 1,5-hexadienes with $KMnO_4$ supported on $CuSO_4.5H_2O$ and in the presence of catalytic amount of water and tert.butyl alcohol has been found to be interesting and the results of this unusual reaction are summarized in **Table IIB.2.1.**

Simple 1,5-hexadiene **1** (2 mmol) when treated with $KMnO_4$ (8 g), $CuSO_4.5H_2O$ (4 g), water (400 μL) and tert.butyl alcohol (2 mL) in dichloromethane (20 mL), at 28 °C for 4 h, afforded hydroxy lactone **11**[10] in 19% yield as the only isolable product. Under similar reaction condition, geranyl acetate **12** on treatment with $KMnO_4/CuSO_4.5H_2O$ and catalytic amount of water/tert.butyl alcohol for 5 h, yielded keto-lactone **14** as the major product (62%) and small amount of 6-membered lactone **15a** (8%) **(Scheme IIB.2.1).** On the other hand, neryl acetate **13**, which is a geometrical isomer of geranyl acetate, upon treatment with $KMnO_4/CuSO_4$ and catalytic amount of water/tert.butyl alcohol in dichloromethane at 28 °C for 5 h, gave keto-lactone **14** as the major product (59%) and small amount of 6-membered lactone **15b** (10%), which is a diastereoisomer of **15a (Scheme IIB.2.1).** Diene **16**, under similar conditions afforded keto-lactone **17** in 47% yield.

Formation of the butanolide derivatives in heterogeneous permanganate oxidation of 1,5-hexadienes with $KMnO_4/CuSO_4.5H_2O$ can be explained by invoking organomanganese intermediate

Scheme -II B-2.1

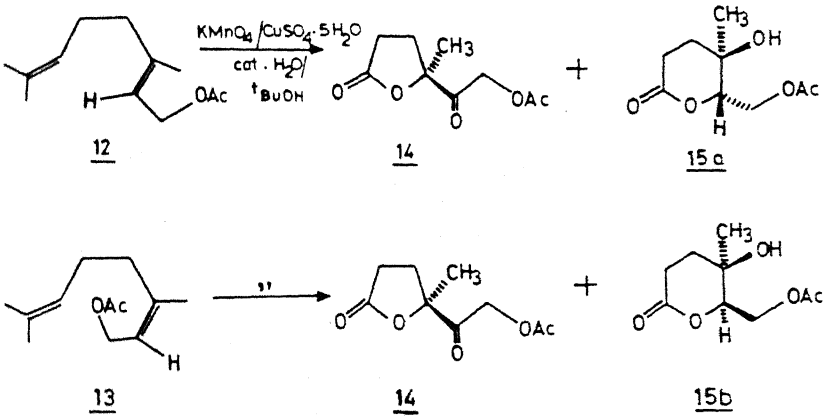
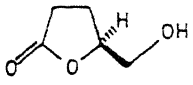
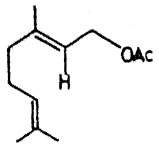
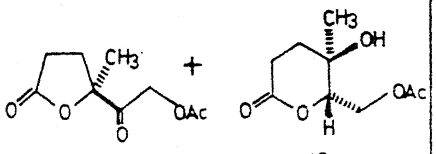
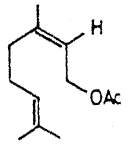
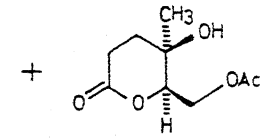
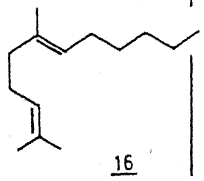
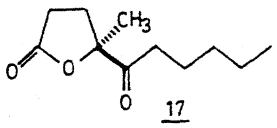
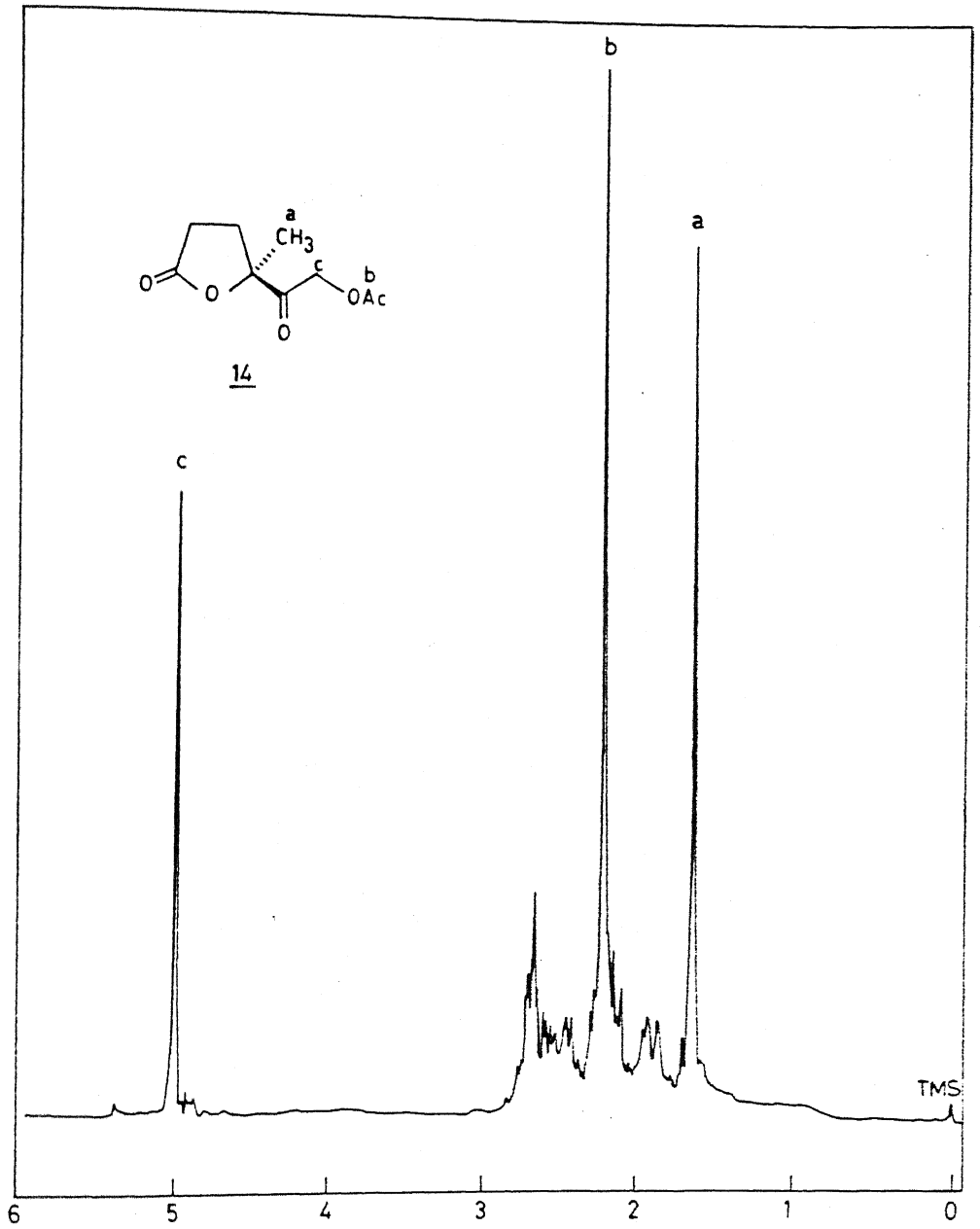
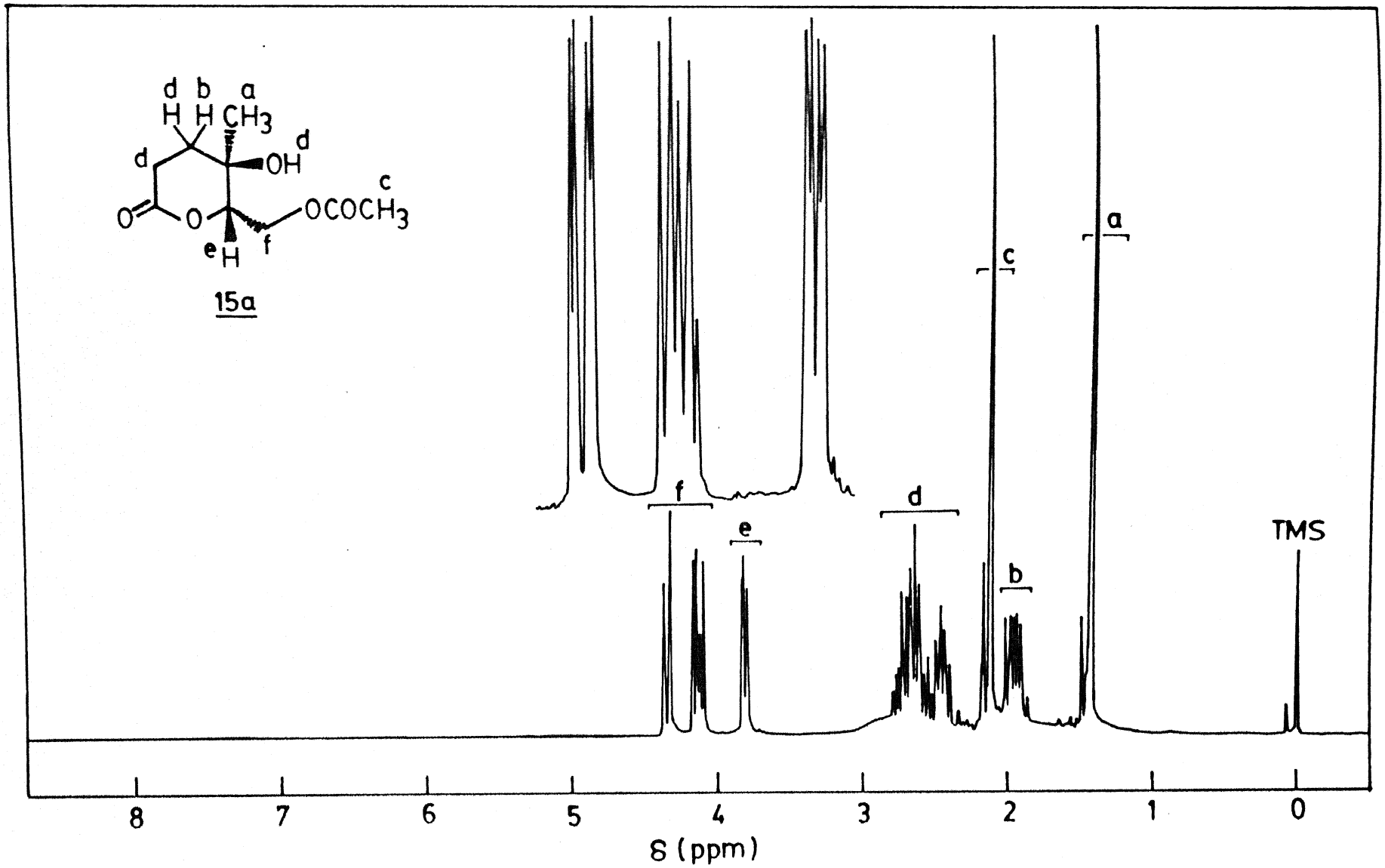


Table -II B-2.1

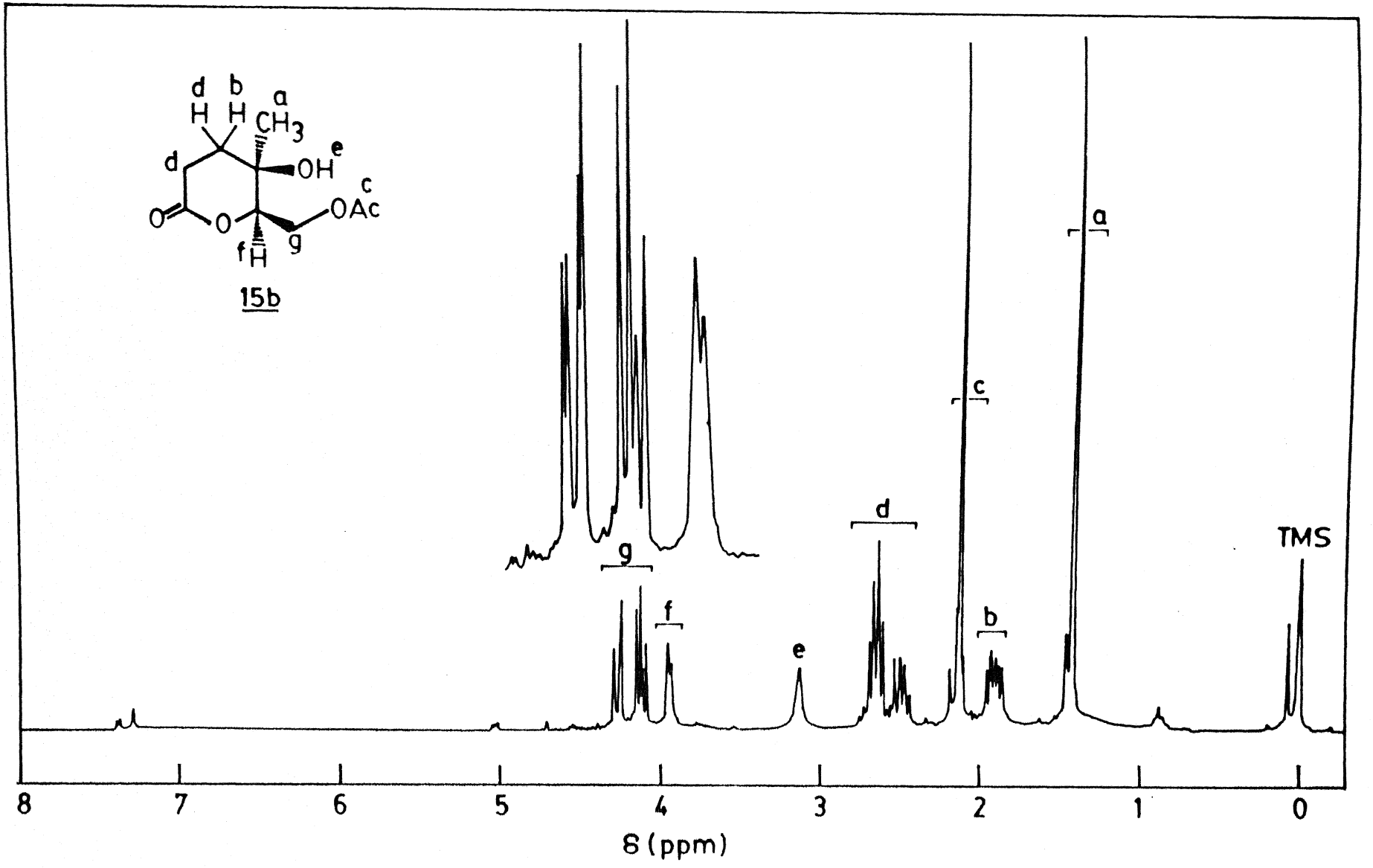
Diene	Product	Yield (%)
1.  1	 11	19
2.  12	 14 : 15a = 6 : 1	60
3.  13	 14 : 15b = 5 : 1	63
4.  16	 17	47



^{1}H NMR Spectrum (80 MHz) of 14



^{1}H NMR Spectrum (250 MHz) of 15a



^{1}H NMR Spectrum (250 MHz) of 15b

proposed by Sharpless[3] and successfully applied by Walba.[4] This pathway illustrated in the reaction of geranyl acetate is outlined in **Scheme IIB.2.2.**

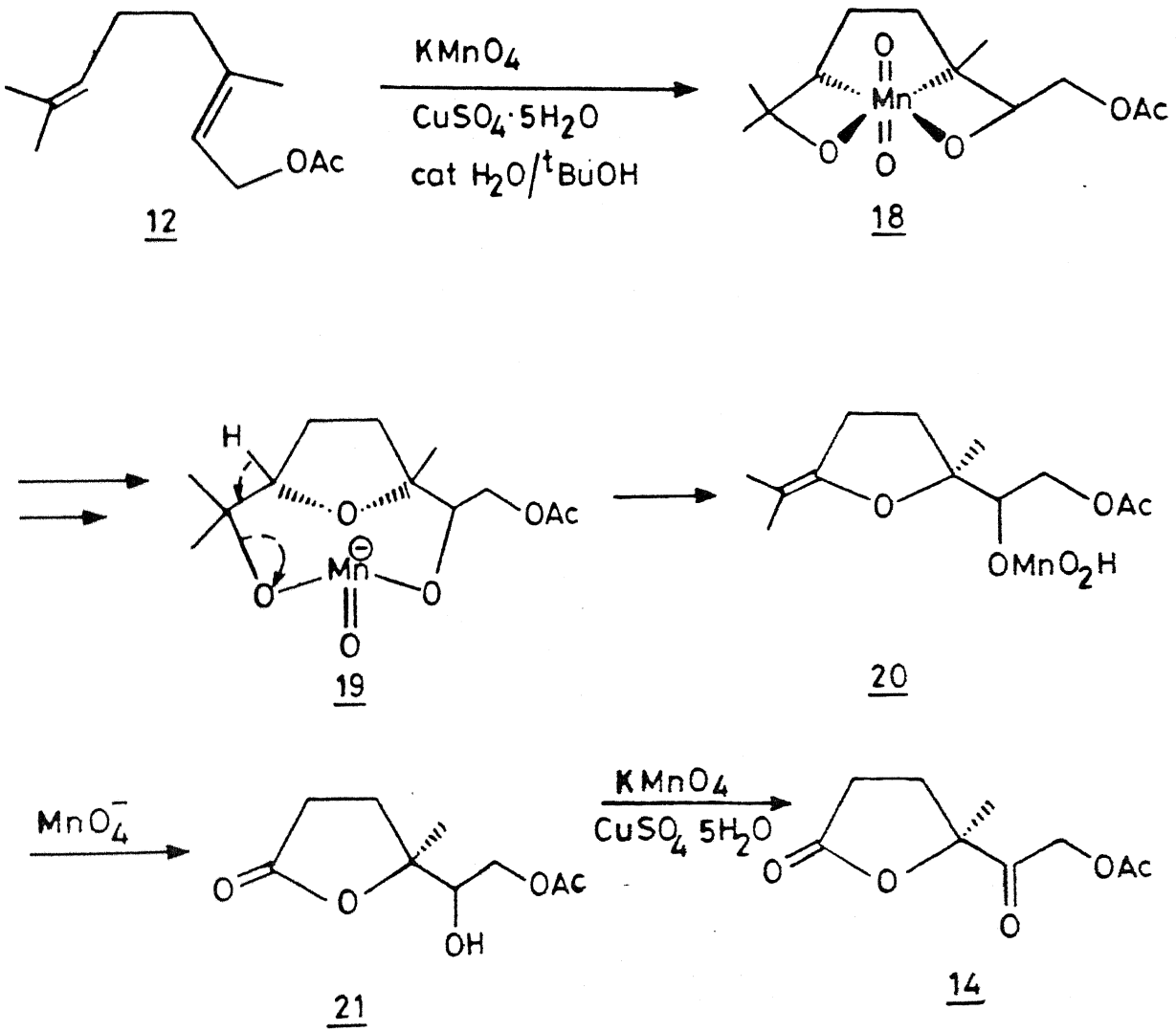
Application of Sharpless proposal[3] in this case would lead to the formation of manganese(IV) ester **19** *via* manganese(VII) ester **18.** Under heterogeneous conditions, this may undergo elimination to give the exocyclic enol ether **20** which subsequently gets oxidatively cleaved with excess permanganate reagent to yield the hydroxy lactone **21.** Secondary alcohols are known[8] to undergo oxidation on treatment with $KMnO_4/CuSO_4.5H_2O$ and thus **21** on further oxidation leads to **14.**

Although the above proposed mechanism accounts for the formation of keto-lactone **14,** it fails to explain the formation of the minor products, the 6-membered lactones **15a** and **15b.**

By invoking Wolfe[6] and Baldwin[5] proposals, formation of the major product keto-lactone **14** and the minor products **15a** and **15b** can be explained and this is shown in **Scheme IIB.2.3.**

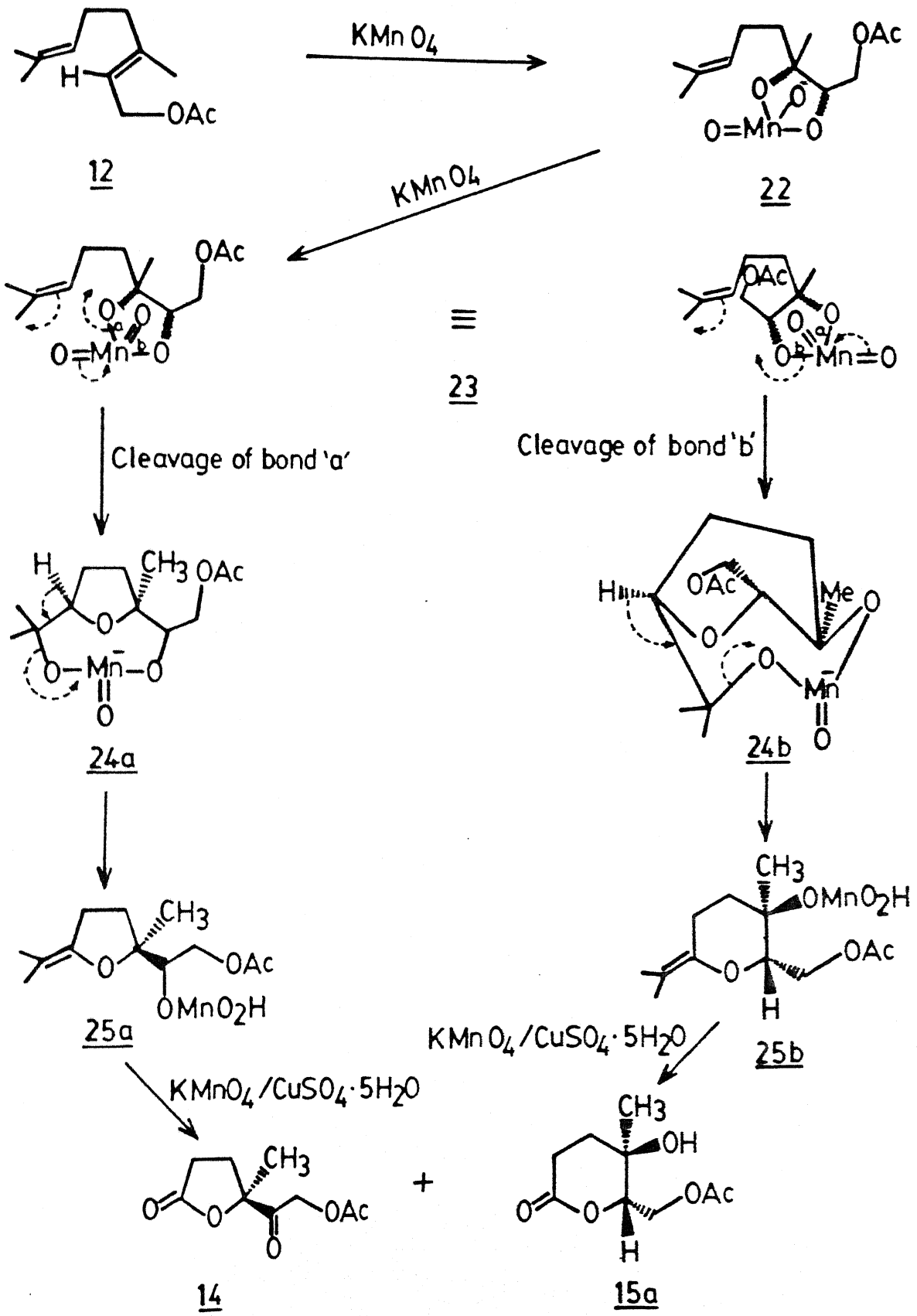
These proposals favor a sequential oxidation[4,6] of the two double bonds *via* a manganese(VI) ester **23.** Intramolecular cycloaddition of the manganese(VI) ester **23,** generated from an initially formed manganese(V) ester **22** by rapid oxidation with permanganate,[9] to the remaining olefinic double bond would lead to the formation of manganese(III) ester **24a** or **24b.** In the oxidation of second double bond by manganese(VI) ester by the reductive cleavage of Mn-O bond **'a'**, would lead to the formation of manganese(III) **24a,** and manganese(III) ester **24b** would arise

Scheme-IIB 2.2



12 18 19 20 21 14

Scheme-IIB-2.3



by the reductive cleavage of Mn-O bond **'b'**. Under heterogeneous conditions, **24a** and **24b** can possibly undergo elimination to give enol ethers **25a** and **25b**, which on further oxidation with excess oxidant would lead to the keto-lactone **14** and 6-membered lactone **15a**, respectively.

In spite of the fact that the mechanism of this novel transformation is speculative at this stage, it is evident that the oxidation of 1,5-dienes with permanganate under condition of omega phase catalysis to form 5-substituted butanolides would prove to be a useful methodology in organic synthesis.

IIB.3 EXPERIMENTAL

General Procedure

As described in Chapter IA.

Materials

As described in Chapter IIA.

Chromatography

As described in Chapter IA.

Physical Data

As described in Chapter IA.

Reaction of 1,5-Hexadiene with $KMnO_4$-$CuSO_4.5H_2O$

A mixture of solid $KMnO_4$ (8.0 g) and $CuSO_4.5H_2O$ (4.0 g) was ground to a fine powder in a pestle and mortar. To this, water (400 μL) was added and the slightly wet mixture was

transferred to a reaction flask. To a stirred suspension of this mixture in CH_2Cl_2 (15 mL) was added 1,5-hexadiene **1** (0.329 g, 4 mmol) in CH_2Cl_2 (5 mL) followed by t-BuOH (2 mL) . Within a few minutes the reaction mixture started to reflux for a while (5 min) and then cooled down. After stirring the reaction mixture for 4 h at room temperature (28 °C) it was filtered over a pad of Celite, washed thoroughly with CH_2Cl_2 and solvent was evaporated. The residue was subjected to silica gel chromatography. Elution of the column with (1:1) ethyl acetate-petroleum ether (60-80 °C) furnished the γ-(hydroxymethyl)-γ-butyrolactone **11**[10] (0.088 g, 19%) as a colorless oil.

IR (neat) : 3460, 1770 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 2.15-2.30 (m, 2 H), 2.52-2.68 (m, 2 H), 3.08 (br,s, 1 H), 3.65 (dd, 1 H), 3.90 (dd, 1 H), 4.62-4.67 (m, 1 H).

MS (m/e) : 117 (m^++1), 85, 57.

Preparation of Geranyl acetate[2] 12

To a stirred solution of geraniol (4.63 g, 30 mmol) in 20 mL of dry CH_2Cl_2 was treated with acetic anhydride (6.12 g, 60 mmol), triethylamine (4.55 g, 45 mmol) and DMAP (0.367 g, 3 mmol). After the usual work-up, the crude product was purified by flash chromatography on silica gel (1:10 ethyl acetate-petroleum ether (60-80 °C) to afford a sweet smelling liquid (5.65 g, 96%)

IR (neat) : 3020, 1735, 1670 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.6 (s, 3 H), 1.7 (s, 6 H), 1.95 (s, 3 H), 2.03 (br, s, 4 H), 4.45 (s, 1 H), 4.52 (s, 1 H), 5.10

(br, s, 1 H), 5.20-5.38 (t, 1 H).

Preparation of Neryl acetate[2] 13

Nerol (4.63 g, 30 mmol) under similar reaction conditions afforded neryl acetate **13** (5.65 g, 96%), after chromatographic purification on silica gel (elution with ethyl acetate-petroleum ether, 1:10).

IR (neat) : 3020, 1730, 1670 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.6 (s, 3 H), 1.7 (s, 3 H), 1.8 (s. 3 H), 1.95 (s, 3 H), 2.05 (m, 4 H), 4.50 (s, 1 H), 4.60 (s, 1 H), 5.10 (br, s, 1 H), 5.20-5.38 (t, 1 H).

Oxidation of Geranyl acetate 12 with $KMnO_4$-$CuSO_4.5H_2O$

A mixture of solid $KMnO_4$ (8.0 g) and $CuSO_4.5H_2O$ (4.0 g) and water (400 µL) in dichloromethane (25 mL) was treated with geranyl acetate **12** (0.392 g, 2 mmol) in dichloromethane (5 mL) and tert.butyl alcohol (2 mL). After 6 h, the reaction mixture was filtered over a pad of Celite and washed thoroughly with dichloromethane. The product, on purification by chromatography using 1:3, ethyl acetate-petroleum ether (60-80 °C) as an eluent furnished the 5-membered keto-lactone **14** (0.248 g, 62%) and 6-membered lactone **15a** (0.032 g, 8%) respectively.

compound 14

IR (neat) : 1775, 1740, 1720 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.53 (s, 3 H), 2.05-2.09 (m, 1 H), 2.12 (s, 3 H), 2.50-2.59 (m, 3 H), 4.88 (s, 2 H).

MS (m/e) : 200, 185, 172, 156.

compound 15a

IR ($CHCl_3$) : 3470, 1740, 1735 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.43 (s, 3 H), 1.93-1.98 (m, 2 H), 2.12 (s, 3H), 2.60-2.72 (m, 3 H), 3.79-3.83 (dd, 1 H), 4.09-4.16 (dd, 1 H), 4.32-4.36 (dd, 1 H).

MS (m/e) : 203 (M^++1), 143, 129, 99, 43.

Anal. Calcd for $C_9H_{14}O_5$: C, 53.47; H, 6.93.
Found: C, 53.57; H, 6.98.

Oxidation of Neryl acetate 13 with $KMnO_4$-$CuSO_4.5H_2O$

Neryl acetate (0.392 g, 2 mmol) was treated under similar conditions (vide supra) with $KMnO_4$ (8.0 g), $CuSO_4.5H_2O$ (4.0 g), water (400 μL) and tert.butyl alcohol (2 mL). From the reaction mixture the keto-lactone **14** (0.236 g, 59%) and 6-membered lactone **15b** (0.040 g, 10%)were isolated, after chromatography on silica gel.

compound 14

IR (neat) : 1775, 1740, 1720 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.53 (s, 3 H), 2.05-2.09 (m, 1 H), 2.12 (s, 3 H), 2.50-2.59 (m, 3 H), 4.88 (s, 2 H).

MS (m/e) : 200, 185, 172, 156.

compound 15b

IR ($CHCl_3$) : 3460, 1740, 1735 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.41 (s, 3 H), 1.81-1.97 (m, 2 H), 2.13 (s, 3 H), 2.56-2.65 (m, 2 H), 3.18 (br,s, 1 H), 3.91-3.98 (br,d, 1 H), 4.08-4.17 (dd,

1 H), 4.22-4.31 (dd, 1 H).

MS (m/e) : 203 (M^++1), 143, 129, 99, 43.

Anal. Calcd for $C_9H_{14}O_5$: C, 53.47; H, 6.93.

Found: C, 53.52; H, 6.90.

Preparation of 2,6-Dimethyldodeca-2,6-diene (16)

6-Methyl-hept-5-en-2-one[11] (1.26 g, 10 mmol) in dry tetrahydrofuran (5 mL) was added dropwise with stirring to the ylid generated *in situ* from hexyltriphenylphosphonium bromide (5.55 g, 13 mmol) and n-butyl lithium (0.769, 12 mmol, 7.5 mL) in dry tetrahydrofuran (10 mL) at 10 °C under nitrogen. After stirring for 2 h at room temperature, ether (30 mL) and water (5 mL) were added and the aqueous layer was extracted with ether. The combined extracts were dried over magnesium sulphate and solvent was evaporated. The crude product was purified by chromatography on silica gel (1:20, ether-petroleum ether, 60-80 °C), to afford 2,6-dimethyldodeca-2,6-diene **16** (1.40 g, 72%) as a colorless oil.

IR (neat) : 3010, 1660 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 0.80-0.97 (t, 3 H), 1.3 (br,s, 6 H), 1.60 (s, 6 H), 1.69 (s, 3 H), 1.97-2.12 (m, 6 H), 5.09-5.31 (br,t, 2 H).

MS (m/e) : 194, 151, 123, 69.

Oxidation of 2,6-Dimethyldodeca-2,6-diene 16

To a mixture of $KMnO_4$ (8.0 g), $CuSO_4.5H_2O$ (4.0 g), water (200 μL) and *tert*.BuOH (2 mL) in dichloromethane (10 mL) was added compound **16** (0.388 g, 2 mmol) in dichloromethane (2 mL)

and stirred for 6 h. On chromatographic purification, the keto-lactone **17** (0.186 g, 47%) was obtained, as a colorless oil.

IR (neat) : 1770, 1720 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 0.70-0.89 (t, 3 H), 1.26 (br,s, 6 H), 1.43 (s, 3 H), 2.05-2.1 (m, 2 H), 2.16-2.53 (m,4 H).

MS (m/e) : 198, 183.

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CHAPTER IIC

IMPROVED PROCEDURE FOR THE PREPARATION OF CETYLTRIMETHYL-AMMONIUM PERMANGANATE (CTAP)

IIC.1 INTRODUCTION

The versatility of permanganate as an oxidant has been greatly enhanced in the past decade by the observation that it can be solubilized in nonaqueous solvents with the aid of phase transfer agents.[1,2] The phase transfer agents that have been used for these purposes include quaternaryammonium and phosphonium ions,[3] crown ethers[4,5] and linear polyethers.[4,5] Several procedures have been described in which quaternaryammonium permanganates are preformed and isolated as semistable solids that can be used as a general oxidants in a wide variety of solvents.[7]

Cetyltrimethylammonium permagnate **I** (CTAP),[8] which is developed from our laboratories, has been found to be a quite stable and readily soluble in dichloromethane and can be handled safely.[9] The superior ability of this quaternaryammonium ion to promote the solubility of permanganate may be attributed to a "penetration effect" which allows the anion to be located close to the center of the cation and, thereby, to be partly shielded from the solvent by the organophilic ligands on the cation.[1]

Cetyltrimethylammonium permanganate **I** (CTAP) has been found

to be an efficient reagent for cis-hydroxylation[8] under anhydrous conditions (**Scheme IIC.1.1**).

This reagent has also been used for the selective oxidation of benzylic alcohols[10] in the presence of primary, secondary and allylic alcohols.

Other important conversions brought about, by this versatile reagent, include: (i) primary, secondary and tertiary γ-hydroxy olefins to lactones,[11] (ii) regeneration of carbonyl compounds from oximes,[12] (iii) cleavage of benzylic double bonds,[13] (iv) nitro to carbonyl functions,[14] and (v) in the natural product synthesis[15] (**Scheme IIC.1.1**).

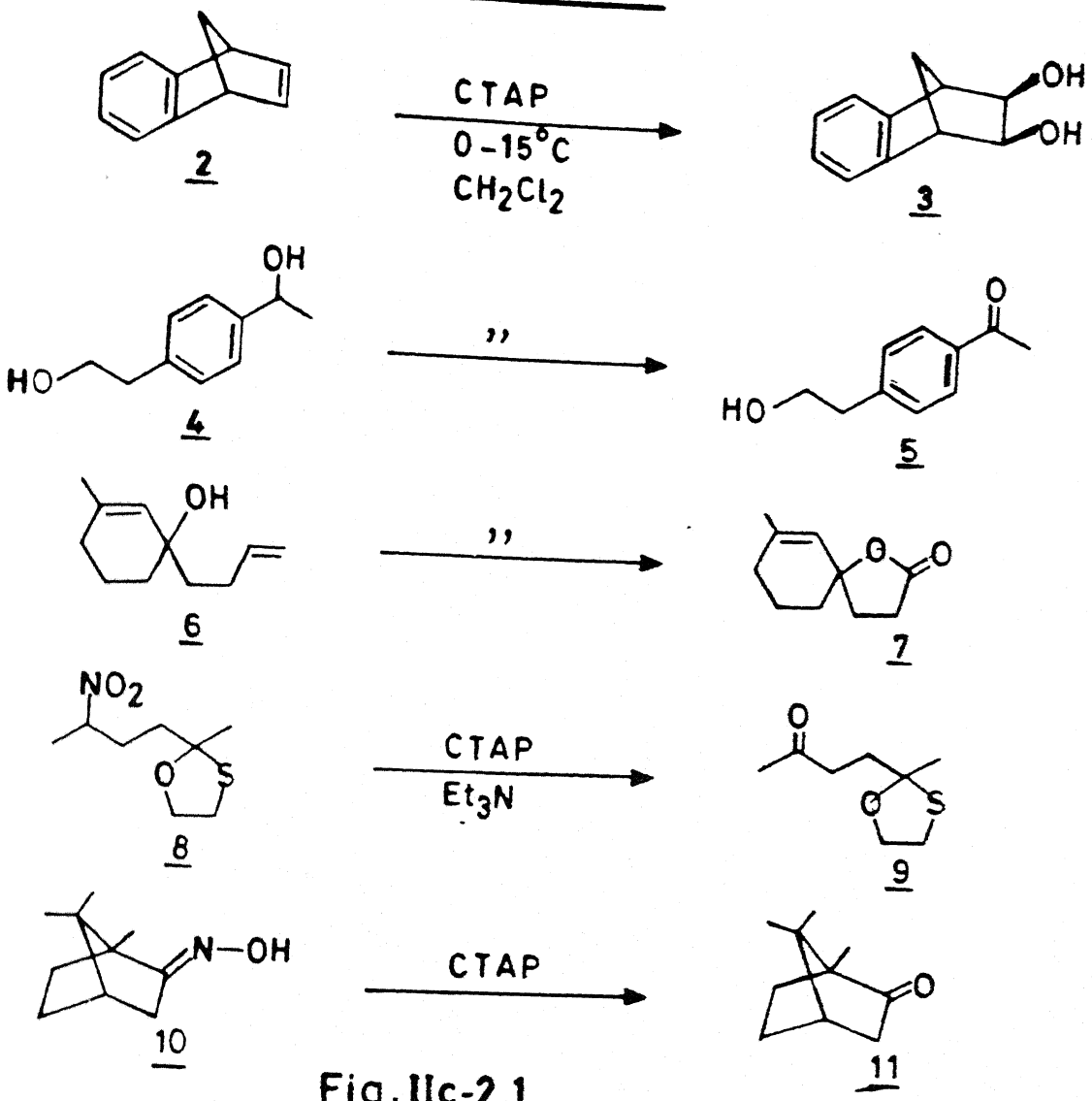
Recently, Freeman[16] reported the kinetic studies on the oxidation of olefins with cetyltrimethylammonium permanganate and it was suggested that permanganate ion adds on to the carbon-carbon double bond in 1,3-dipolar manner.

Although the reported procedure[8] for the preparation of cetyltrimethylammonium permangnate works very well on small scale, scaling up is very difficult and it involves tedious filtration procedure.

Since the application[17] of this reagent in organic synthesis, keeps on increasing, there was a need for modification of the reported procedure for large scale preparation.

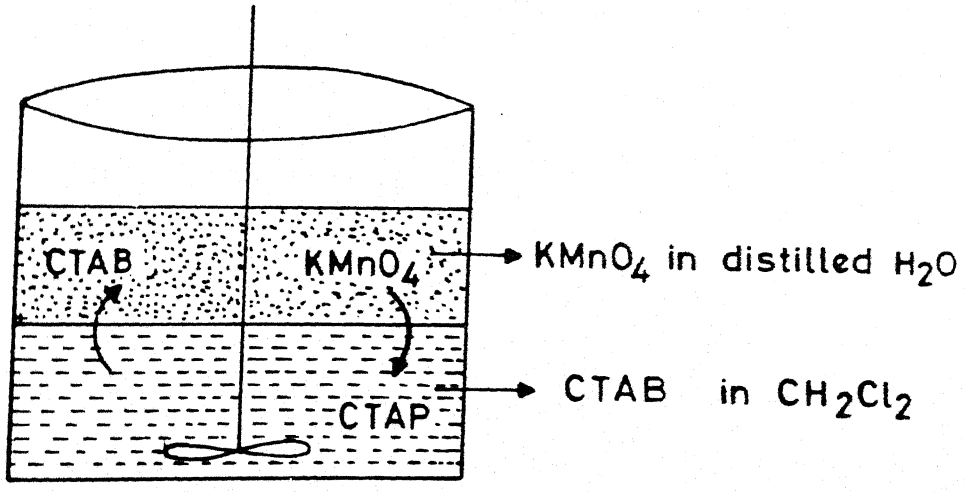
In the present study, a simple procedure has been developed for the preparation of CTAP on large scale.

Scheme-IIc-1.1



2 3 4 5 6 7 8 9 10 11

Fig.IIc-2.1



Preparation of CTAP

IIC.2 RESULTS AND DISCUSSION

We developed a simple and effective method for the preparation of cetyltrimethylammonium permanganate, CTAP, on large scale by taking into account three important factors i.e.,

i) $KMnO_4$ is soluble only in water,

ii) CTAB is soluble in water as well as in CH_2Cl_2,

iii) CTAP is soluble only in CH_2Cl_2.

By considering the above three points, we used two phase system i.e., water and CH_2Cl_2 for the preparation of CTAP (**Fig. IIC.2.1**).

A mixture of $KMnO_4$ in distilled water and CTAB in distilled CH_2Cl_2 was stirred vigorously, until a clear separation of the layers was achieved. CH_2Cl_2 was removed under vacuum, filtered and dried over P_2O_5 to yield CTAP, as a crystalline purple solid; m.p. 86 ^oC.

IIC.3 EXPERIMENTAL

In a two-necked round bottomed flask (2 L) equipped with an efficient mechanical stirrer, and a stopper, is placed potassium permanganate (note 1) 42.67 g (270 mmol) in 250 mL of distilled water. The flask and contents are cooled to 8-10 ^oC in an ice-salt bath and 91.12 g (250 mmol) of cetyltrimethylammonium bromide (note 2) in 500 mL of distilled dichloromethane is added over a period of about 5 min. with vigorous stirring. While

the temperature is kept at 8-10 °C, the resulting mixture is stirred vigorously, until a clear separation of the two layers is achieved (3-4 h) (note 3). Dichloromethane is removed under vacuum and granules of cetyltrimethylammonium permanganate in water is filtered through a Buchner funnel, washed thoroughly with distilled water (2 L), then with dry ether (2x100 mL) and dried over P_2O_5 under vacuum to give cetyltrimethylammonium permanganate (CTAP) as a crystalline purple solid, m.p. 86 °C (lit.[8] m.p. 86 °C).

Notes:

(1) Potassium permanganate obtained from Merck & Co., Inc., was used as such.

(2) Cetyltrimethylammonium bromide was obtained from Aldrich Chemical Co., Inc. and used without further purification.

(3) If the separation of the two layers is not clear even after 4 h, separation can be achieved by the addition of excess potassium permanganate (10 mmol).

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CHAPTER III

NEW SYNTHETIC METHODOLOGY WITH BENZYLTRIETHYLAMMONIUM BOROHYDRIDE CHLOROTRIMETHYLSILANE

III.1 INTRODUCTION

Modified Borohydride Reagents:

Sodium borohydride is a mild reducing agent with high selectivity.[1] The tetrahydroborate ion and its derivatives have found extensive use as selective reducing agents in both organic[2] and organometallic[3] synthesis. In addition, BH_4^- has been utilized as a ligand to form covalent coordination complexes[4] which are of both theoretical and practical interest because of the unusual bonding modes exhibited by the borohydride moiety,[5] their fluxional behavior[6] and their catalytic properties.[7]

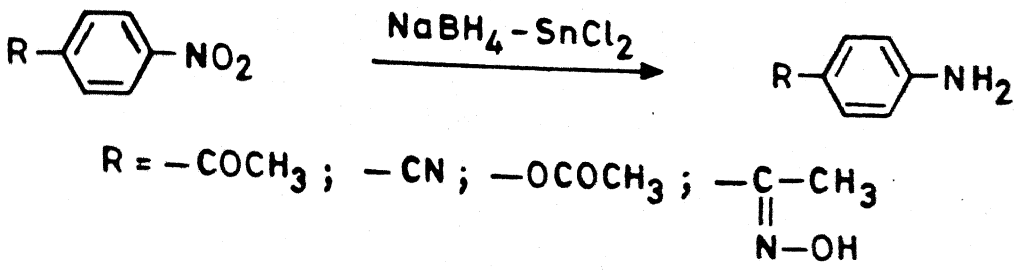
It has been observed that the reducing ability of sodium borohydride can be increased by the addition of metal salts such as LiCl,[8] $AlCl_3$[9] and $MgCl_2$.[10] Sodium borohydride, in combination with any one of these salts, is capable of reducing esters and lactones which are inert towards $NaBH_4$.

More recently, several transition metal halides have been found to be effective for the activation of sodium borohydride. These reducing agents have been used for the reduction of various functional groups and these reactions have attracted

considerable attention in organic synthesis.[11] Although $NaBH_4$ is inert towards nitrile, amide and nitro functional groups, in the presence of $CoCl_2.6H_2O$, these functional groups can be converted to the corresponding amines.[12] Halides, sulfates and carboxylates of cobalt, nickel, rhodium, osmium and platinum can also be advantageously used as metal salts of the reducing systems instead of $CoCl_2$.[12] $PdCl_2$-$NaBH_4$, $CuCl_2.2H_2O$-$NaBH_4$, $NiCl_2.6H_2O$-$NaBH_4$ and $CoCl_2.6H_2O$-$NaBH_4$ have been used for the selective hydrogenation of carbon-carbon double bonds in unsaturated esters.[13] $ZrCl_4$-$NaBH_4$[14] has been found to be an excellent reagent for the reduction of olefins. Conversion of dienes to olefins has also been achieved[15] by the use of $CoCl_2$-$NaBH_4$ and $CuCl_2$-$NaBH_4$. $PdCl_2$ in combination with $NaBH_4$[16] has been used for the reduction of aryl ketones, aryl chlorides, and benzylic alcohols to the corresponding hydrocarbons. $NaBH_4$ in presence of catalytic amount of palladium on carbon[17] has been used for the reduction of nitro compounds to the corresponding amines. It was also reported that $NaBH_4$ in presence of rhodium chloride complexes with pyridine,[18] gives a homogeneous system which readily reduces aromatic nitro compounds to aniline derivatives. The $NaBH_4$-$SnCl_2$[19] system also belongs to the homogeneous category and shows very high selectivity for aromatic nitro groups even in the presence of nitrile, ketone, olefin, and oxime functional groups, which are known to be reduced easily by treatment with $NaBH_4$ or $NaBH_4$-transition metal salts (**Scheme III.1.1**).

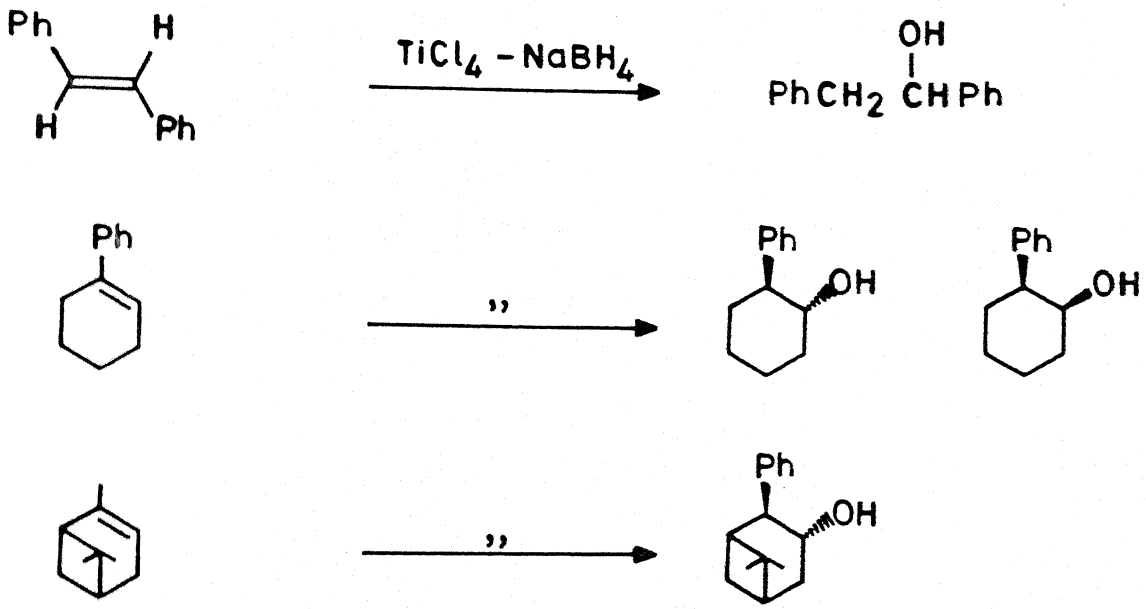
Very recently, $SnCl_4$-$NaBH_4$[20] and $TiCl_4$-$NaBH_4$[21] have been found to be useful reagents for effecting the direct conversion

Scheme III.1.1

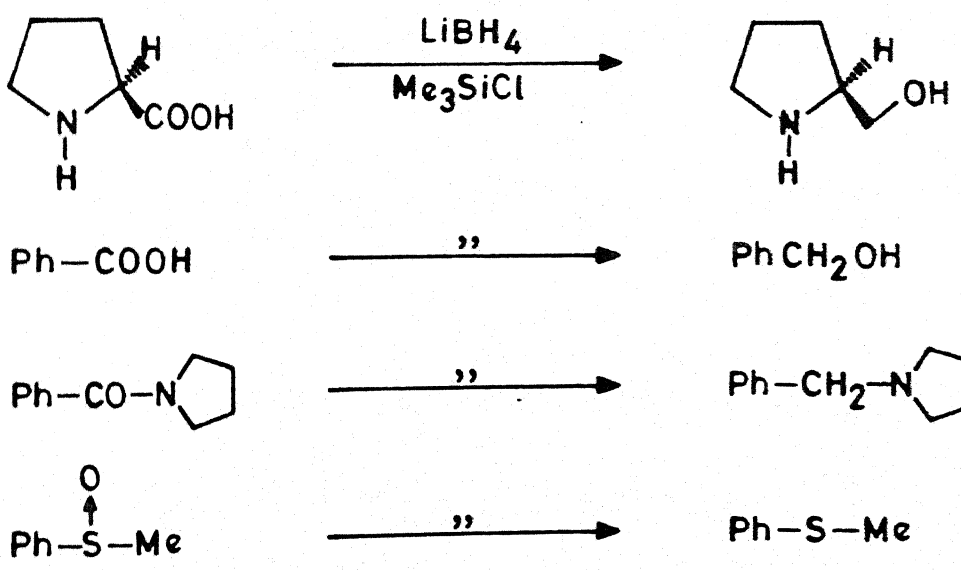


R = $-COCH_3$; $-CN$; $-OCOCH_3$; $-C(=N-OH)-CH_3$

Scheme III.1.2



Scheme III.1.3



of alkenes to alcohols, the hydroxyl group of which is introduced in a anti-Markovnikov direction (**Scheme III.1.2**). $TiCl_4$-$NaBH_4$[21] system has also been used for the reduction of variety of functional groups such as carboxylic acids to alcohols, amides to amines, oximes to amines, sulfoxides to sulfides and nitrosamines to secondary amines.[22]

Borohydrides have also been activated by chlorotrimethylsilane. Me_3SiCl-$Zn(BH_4)_2$[23] reducing system has been used for the reductive cleavage of acetals and ketals. Selective reduction of aldehydes in presence of ketones has been reported with Me_3SiCl-Ni_2B system.[24] More recently, $LiBH_4$-Me_3SiCl[25] has been found to be an excellent reducing system for the reduction of carboxylic acids to alcohols, amino acids to amino alcohols, amides to amines, nitriles to amines and sulfoxides to sulfides (**Scheme III.1.3**).

Sodium borohydride reactions are usually carried out in hydroxylic solvents, as non-hydroxylic solvents cannot be used due to the lack of solubility. The ability to carry out borohydride reduction in non-hydroxylic solvent would nevertheless be quite useful. For instance, the reduction of aldehydes and ketones with sodium borohydride in the commonly employed aqueous or alcoholic solvents can be complicated by side reactions such as the formation of hydrates, acetals, ketals or ether.[26] One of the ways of overcoming this problem is by the use of tetraalkylammonium borohydrides.[27-29] The high solubility of these reagents in dichloromethane permit reductions to be carried out in high yields in the absence of protic solvents.

Tetraalkylammonium borohydride reduces acid chlorides and aldehydes very rapidly, whereas ketones are reduced at convenient rates and esters are reduced quite slowly.[28]

Tetraalkylammonium borohydrides have also been used for the generation of pure diborane in dichloromethane.[29] Quaternary-ammonium borohydride yields diborane, on treatment with electrophiles such as methyl iodide, ethyl bromide or 1,2-dichloroethane, which can be conveniently used for the hydroboration reaction.[29] (Eqn. 1).

$$2\ Q^+B^-H_4 + R\text{-}X \xrightarrow{CH_2Cl_2} 2\ Q^+X^- + 2\ RH + B_2H_6$$

..(Eqn. I)

Hydroboration Reaction

The olefins can be readily and quantitatively converted into organoboranes under exceedingly mild reaction conditions, which on further treatment with alkaline hydrogen peroxide lead to alcohols.[30] The hydroboration reaction provides a convenient procedure for the conversion of olefinic groups into alcohols without rearrangement and with the production of stereochemically defined structures.[31]

Although hydroboration reaction is method of choice for the conversion of olefins to alcohols, substrates having base sensitive functional groups cannot be subjected to hydroboration reaction, which involves the oxidation of organoborane to alcohol under very strong basic conditions. Attempted hydro-

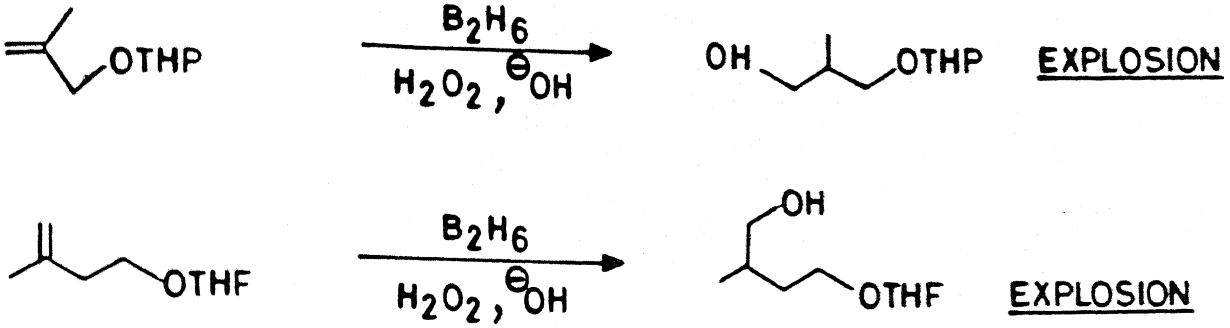
boration-oxidation of olefins containing -OTHP or -OTHF functional group have led to explosions on purification by distillation.[32] This has been attributed to the formation of peroxy intermediates by -OTHP or -OTHF ethers during the oxidative work-up with alkaline hydrogen peroxide (**Scheme III.1.4**).

Hydroboration of Enol Ether Double Bonds

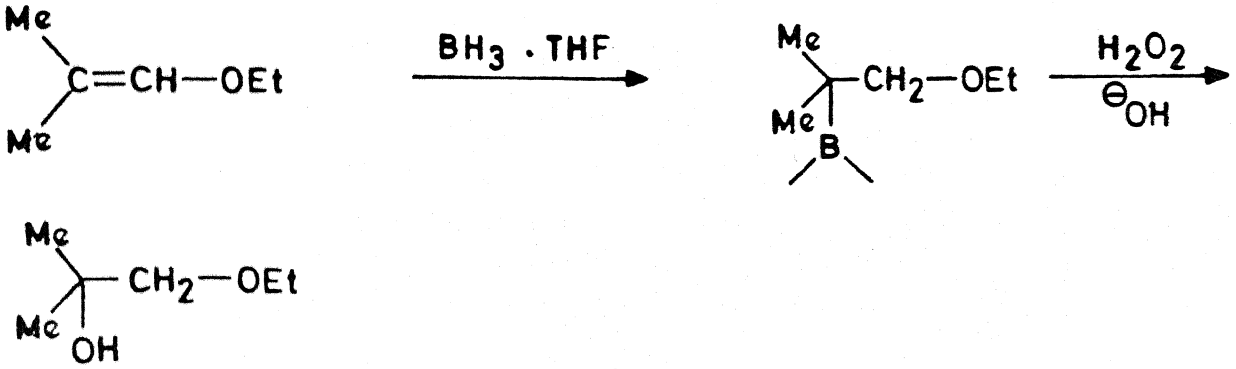
Hydroboration reaction on electron rich enol ether double bond is highly stereo- and regioselective.[33-36] The hetero-oxygen atom directs the addition of diborane nearly exclusively to the β-position[36] (**Scheme III.1.5**). Hydroboration of dihydropyran and dihydrofuran afforded 3-hydroxy tetrahydropyran and 3-hydroxy tetrahydrofuran, respectively as the major product along with small amount of acylic diols.[36] The formation of the acylic diols can be envisaged as proceeding <u>via</u> a BH_3-catalyzed elimination (**Scheme III.1.6**). This produces the unsaturated derivative, which is subsequently rehydroborated to afford after oxidation, the observed diols.[36]

During the course of our investigation with tetraalkylammonium borohydrides, we found that a combination of benzyl triethylammonium borohydride and chlorotrimethylsilane can be conveniently used for the direct conversion of olefins to alcohols. The results we obtained on this unusual transformation and subsequent studies on the electron rich enol ether double bonds will be discussed in this chapter.

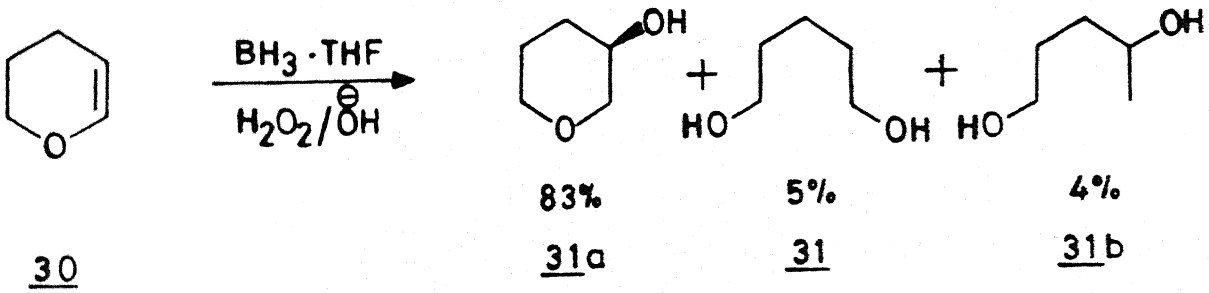
Scheme III.1.4



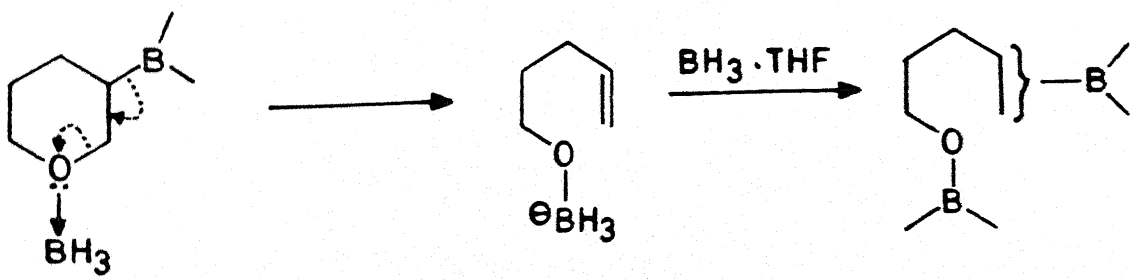
Scheme III.1.5



Scheme III.1.6



Formation of diols:



H_2O_2 / $\ominus OH$ → Diols

III.2 RESULTS AND DISCUSSION

As mentioned earlier, pure diborane can be conveniently prepared in dichloromethane by the addition of an electrophile, such as methyl iodide to tetraalkylammonium borohydride, which can be used directly for the hydroboration reaction.[29] In the course of our investigations, we find an unusual observation, i.e., when chlorotrimethylsilane is used as electrophile, olefins are directly converted to the corresponding alcohols without involving a formal oxidative work-up (**Scheme III.2.1**).

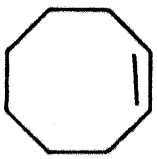
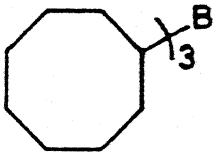
A combination of benzyltriethylammonium borohydride and chlorotrimethylsilane (1:1 eq.)in dichloromethane at 0 ^{o}C reacts with alkenes readily to produce the corresponding alcohols directly in high yields. The hydroxyl group is introduced in a anti-Markonikov manner. The results of the reactions are summarized in **Table III.2.1**. In all the reactions, apart from the major product alcohol, a small amount of the corresponding saturated hydrocarbon (7-18%) is also formed. Olefins **1**, **3** and 5 on treatment with benzyltriethylammonium borohydride and chlorotrimethylsilane, yielded alcohols **2** (80%), **4** (78%) and **6** (74%) respectively in high yields. The terminal olefin **7**, under similar reaction conditions, afforded the primary alcohol **8** (72%) as the only product and it did not form any secondary alcohol. Interestingly 1-phenylcyclohexene **9** gave a mixture of cis- and trans-isomers of 2-phenylcyclohexanol in the ratio of 1:3, in high yields (84%). The trans **10a** and cis **10b** isomers were separated by flash chromatography on silica gel. Thus unlike normal hydroboration, this reaction is not stereo-selective. Similarly (±) α-pinene **11**, under the reaction condi-

Scheme III.2.1

Alkene $\xrightarrow[CH_2Cl_2]{MeI/\overset{+}{Q}\bar{B}H_4}$ Organo borane

Alkene $\xrightarrow[CH_2Cl_2]{\text{i) } Me_3SiCl/\overset{+}{Q}\bar{B}H_4 \text{ ii) } H_2O}$ Alcohol

Scheme III.2.2

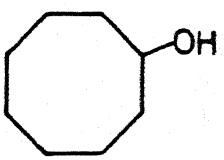
1.  + $PhCH_2\overset{\oplus}{N}Et_3\overset{\ominus}{B}H_4$ $\xrightarrow[CH_2Cl_2, 0^\circ C]{CH_3I}$ 

5 16

2. 5 + $PhCH_2\overset{\oplus}{N}Et_3\overset{\ominus}{B}H_4$ $\xrightarrow[CH_2Cl_2, 0^\circ C]{Bu_3SnCl}$ 16

3. 5 + Free B_2H_6 $\xrightarrow[CH_2Cl_2, 0^\circ C]{Me_3SiCl}$ 16

4. 5 + Free B_2H_6 + $PhCH_2\overset{\oplus}{N}Et_3\overset{\ominus}{Cl}$ $\xrightarrow{\text{"}}$ 16

5. 5 + $PhCH_2\overset{\oplus}{N}Et_3\overset{\ominus}{B}H_4$ $\xrightarrow[CH_2Cl_2, 0^\circ C]{Ph_2\overset{Me}{\overset{|}{S}}iCl}$  + $Ph_2\overset{Me}{\overset{|}{S}}i\text{-}H$

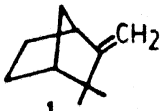
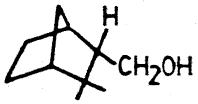
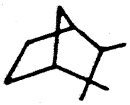
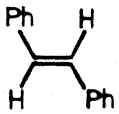
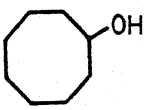
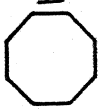
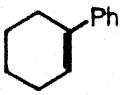
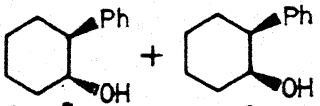
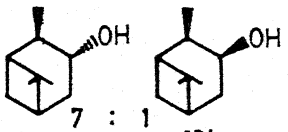
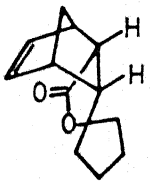
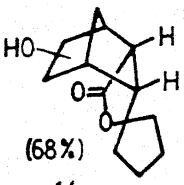
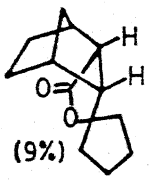
6

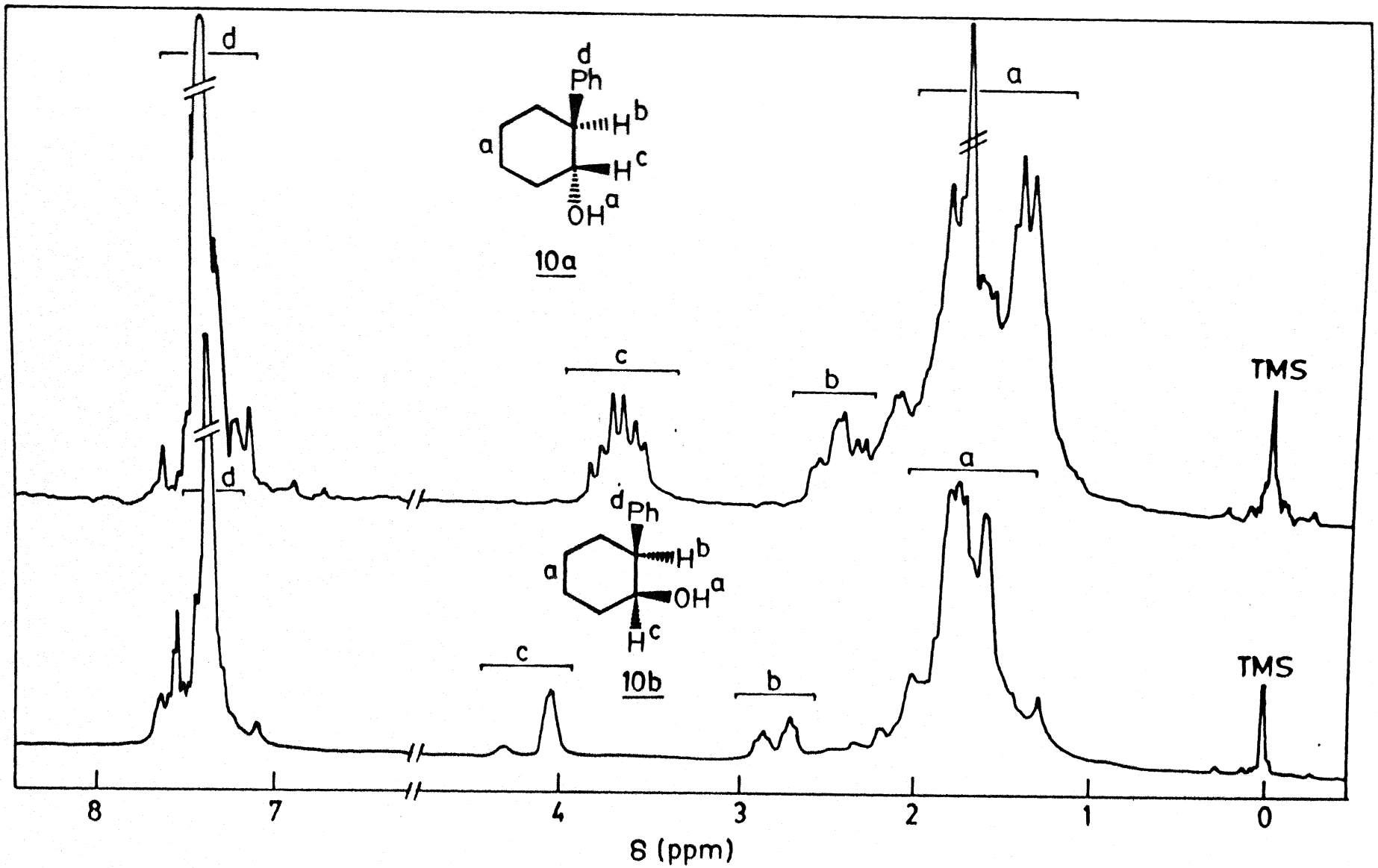
6. 5 + Free B_2H_6 $\xrightarrow[CH_2Cl_2, 0^\circ C]{Et_3SiH}$ 16

7. 5 + $NaBH_4$ $\xrightarrow[DME, 0^\circ C]{Me_3SiCl}$ 6

8. 5 + $PhCH_2\overset{\oplus}{N}Et_3\overset{\ominus}{B}H_4$ $\xrightarrow[CH_2Cl_2, N_2, 0^\circ C]{Me_3SiCl}$ 6

Table-III-2.1

ENTRY	ALKENE	t/h	ALCOHOL	HYDROCARBON
1	 1	3	 (80%) 2	 (17%) 2c
2	 3	8	Ph–CH_2CH(OH)–Ph (78%) 4	Ph–CH_2–CH_2–Ph (8%) 4c
3	 5	0.5	 (74%) 6	 (18%) 6c
4	$Me(CH_2)_6CH=CH_2$ 7	0.5	$Me(CH_2)_7CH_2OH$ (72%) 8	$Me(CH_2)_7Me$ (18%) 8c
5	 9	4	 10a 3 : (84%) 1 10b	 (9%) 10c
6	 (±) 11	3	 12a 7 : 1 (82%) 12b	 (11%) 12c
7	 13	2	 (68%) 14	 (9%) 14c
8	Ph–C≡C–Ph 15	10	Ph–CH_2CH(OH)–Ph (70%) 4	Ph–CH_2–CH_2–Ph (13%) 4c



^{1}H NMR Spectrum (80 MHz) of 10a and 10b

tions, yielded a mixture of (+) isopinocampheol **12a** and (±) neo-isopinocampheol **12b** (82%) in the ratio of 7:1. When the same reaction was carried out on the optically active (+) α-pinene, (-) isopinocampheol (74%) and (+) neo-isopinocampheol (10%) were obtained in good yields. Spirolactone **13**[37] on treatment with this reagent system yielded a mixture of regio-isomeric alcohols **14** (68%), without affecting the lactone moiety. Diphenylacetylene **15**, under similar reaction conditions (10 h), yielded 1,2-diphenylethanol **4** (70%) and small amount of 1,2-diphenylethane **4c** (13%). When the same reaction was interrupted after 3 h, a mixture of trans- and cis-stilbene in the ratio of 2:1 (12%) was isolated. Again in contrast to hydroboration, this reaction is not stereoselective and diphenylacetylene gives trans-stilbene as the major product instead of cis-stilbene.

It appears that one of the pathways by which the saturated hydrocarbons are formed in these reactions as minor product is by deoxygenation of the alcohols under the reaction conditions. This is supported by the fact that when trans-2-phenylcyclohexanol **10a** was treated with benzyltriethylammonium borohydride and Me_3SiCl (1:1) at 0 °C for 2 h, phenylcyclohexane **10c** was obtained in 15% yield.

In order to understand the mechanism of this transformation better, several reactions have been carried out and these are shown in **Scheme III.2.2.** When a mixture of cyclooctene **5** and benzyltriethylammonium borohydride in dichloromethane at 0 °C was treated with methyl iodide (condition under which pure

diborane is generated[29]), the corresponding organoborane **16** was obtained as the only product. This observation clearly shows that silicon plays an important role in our transformation. To get more information about the generality of this reaction, Bu_3SnCl was used instead of Me_3SiCl (tin and silicon belong to the same group); in this case also organoborane **16** was obtained as the only product.

In the third experiment free diborane[29] in dichloromethane was treated with Me_3SiCl and followed by the addition of olefin **5**. Again organoborane **16** was obtained as the sole product. In the next experiment free diborane was treated with benzyltriethylammonium chloride, Me_3SiCl and then with olefin **5**, once again organoborane 16 was obtained. These experiments point out that free diborane in the presence of these additives does not produce the same result as the benzyltriethylammonium borohydride-chlorotrimethylsilane system.

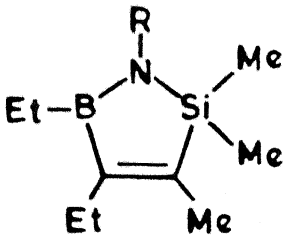
In order to see whether any other chlorosilane would react in a similar fashion, a reaction was performed where olefin **5** was treated with chlorodiphenylmethylsilane-benzyltriethylammonium borohydride (1:1) at 0 °C. In this case, in addition to alcohol **6** (67%) a small amount of diphenylmethylsilane was also obtained as a side product. We thought, the formation of alkylsilane may be playing some role in the overall transformation. In order to verify this, yet another reaction was carried out with **5** free diborane[29] in the presence of triethylsilane (Et_3SiH) and only organoborane **16** was isolated.

A combination of $NaBH_4$ and Me_3SiCl also gave alcohol **6**, although in lower yields (63%). When the reaction of olefin 5 with benzyltriethylammonium borohydride and Me_3SiCl was performed under nitrogen atmosphere, the alcohol **6** was obtained in lower yield (50%). It is likely that oxygen gets incorporated in this reaction from molecular oxygen.

From the above mentioned experimental observations one can safely conclude that simple diborane is not involved in this transformation and silicon plays a major role in this reaction. It is possible that boron and silicon may be forming a reactive species, which reacts with olefin to form a reactive intermediate and this can pick up oxygen from the atmosphere to give the product alcohol.

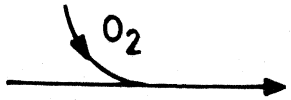
In the light of the recent observation by Koster, the mechanism for the above transformation is provocative and interesting. Koster and Seidel[38] observed that compounds **17a-c** (**Scheme III.2.3**), rapidly take up molecular oxygen at 0-20 ^{o}C and form **18a-c** with high regio-selectivity (80%). The autoxidations, which proceed rapidly and afford pure peroxyboron compounds require the presence of certain atomic groupings in the unsaturated five-membered ring. Compound **19** rapidly takes up one equivalent of O_2, even at -78 ^{o}C. In contrast, compound **20**, which contains the isopropylidene moiety in place of the dimethylsilanediyl group of **19**, does not react with molecular oxygen. Koster proposed[38] that the autoxidation of **17** and **19** proceed <u>via</u> oxygen associates **21** having a bicyclo[2.2.1]heptane structure.

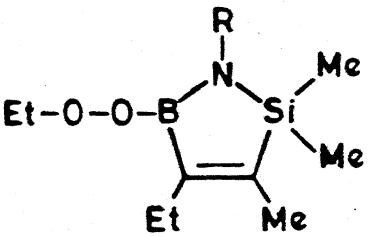
Scheme III.2.3



17 a-c

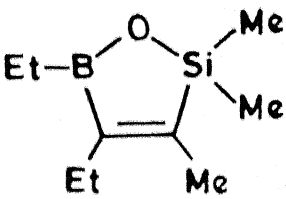
$R = -CH_3$; $-Ph$; $-CH_2Ph$



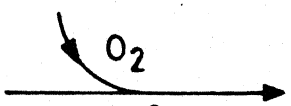


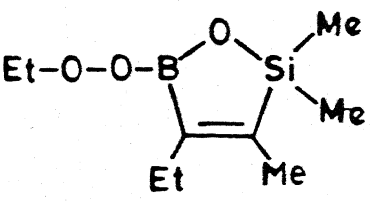
~80%

18 a-c

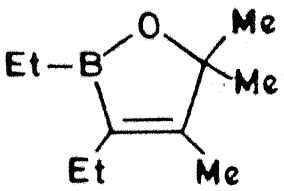


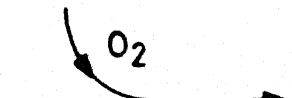
19



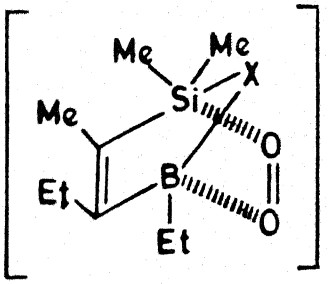


19a





No reaction



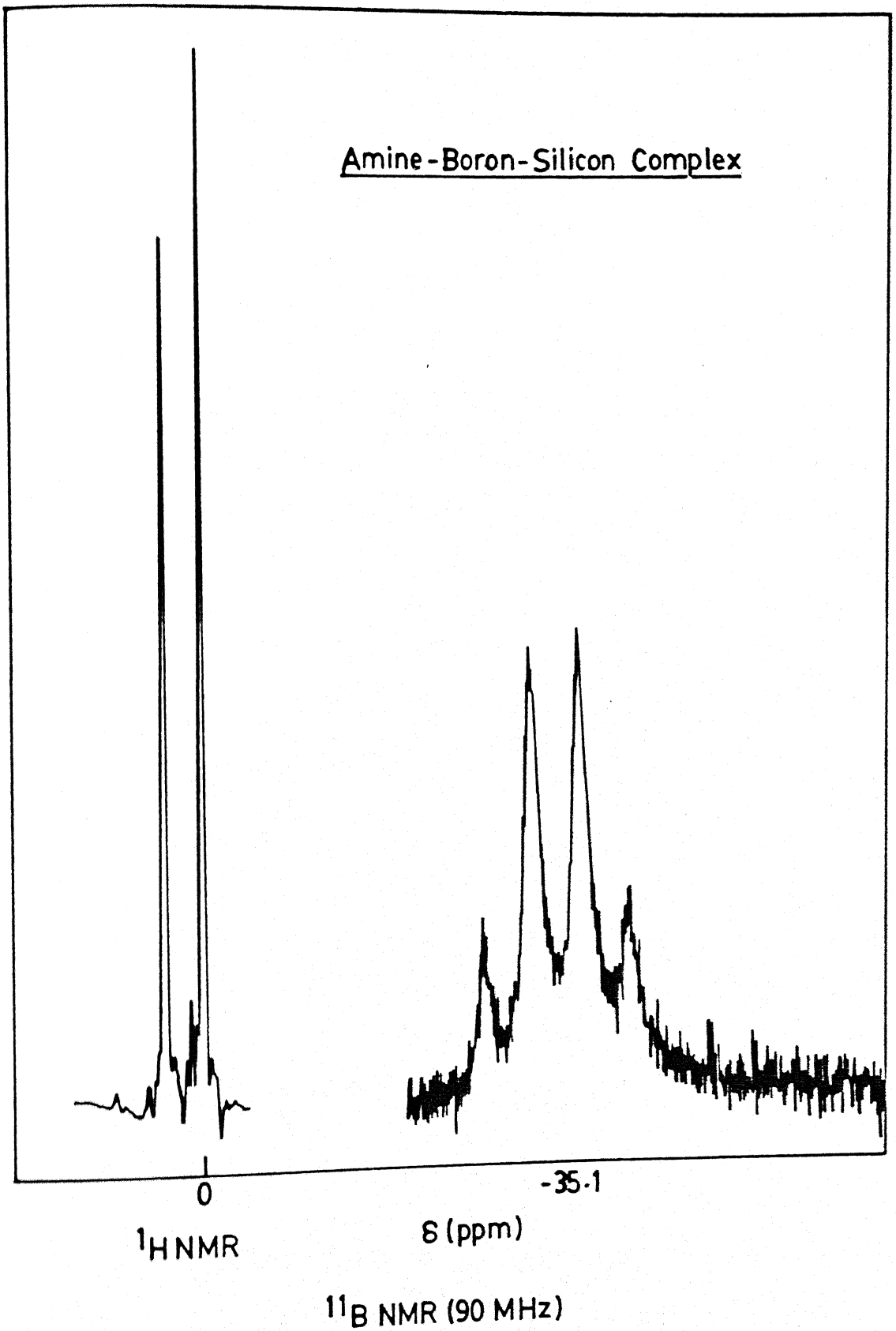
X = NR , O

21

In order to understand the reaction better, attempts to isolate intermediate, if any, have met with failure. However, a reactive species was trapped by adding a small amount of triethylamine to the reaction mixture. It was observed that the reactive species-triethylamine complex is quite stable and it does not react with olefins. Surprisingly, NMR spectral analysis showed the presence of boron and silicon in the complex. ^{11}B NMR gave a quartet at -35.1 ppm, i.e., three hydrogens are attached to boron. When ^{1}H and ^{13}C NMR spectra were recorded in the absence of internal standard tetramethylsilane (TMS), methyl groups attached to silicon signals were obtained at 0.1 to 0.0 ppm.

These observations are in accordance with Koster's[38] findings. We believe, in our case also, the boron-silicon centers may be binding a molecular oxygen, which undergoes alkyl migration to give the peroxo complex. This peroxo complex may undergo reduction to alcohol in the presence of excess borohydride or it may undergo hydrolysis to give alcohol in the presence of moisture. Further work has to be done, in order to substantiate the involvement of silicon in this transformation. Work is in progress with chiral silicon reagents and chiral quaternaryammonium borohydrides, in order to understand the efficacy of this boron-silicon promoted reaction.

At the present stage, the mechanism of this unusual reaction remains unclear, but hydroboration-oxidation can be excluded as the reactivity of this reagent system is considerably different.


Amine-Boron-Silicon Complex
0
-35.1
^{1}H NMR
δ (ppm)
^{11}B NMR (90 MHz)

As mentioned earlier, attempted purification of alcohols, obtained from hydroboration-oxidation of olefins having -OTHP or -OTHF ethers led to explosion[32] (**Scheme III.1.4**). Since benzyltriethylammonium borohydride-Me_3SiCl reagent system directly converts olefins to alcohols without involving the formal oxidative work-up with alkaline hydrogen peroxide, we thought, it would be convenient and safe to use this reagent system for the conversion of olefins having -OTHP or -OTHF ethers to alcohols. As expected compounds **22**, **24** and **26** on treatment with benzyltriethylammonium borohydride, Me_3SiCl (1:1) reagent system, underwent smooth conversion to the corresponding alcohols **23**, **25** and **27** respectively and they could be purified without any difficulty (59-68%) (**Table III.2.2**). Thus this reagent system makes mono protected diols more readily accessible.

Since a combination of benzyltriethylammonium borohydride and chlorotrimethylsilane behaves differently from diborane, we believed, it would be interesting to study the reaction with enol ethers. Surprisingly, when this reagent system was allowed to react with cyclic enol ethers **28**, **30**, **32** and **34**, the corresponding acyclic diols **29**, **31**, **33** and **35** were obtained in very good yields (**Table III.2.3**). 1-Ethoxy 1-heptene **36**, on treatment with this reagent system, afforded 1-heptanol **37** in high yield. In contrast to hydroboration, cyclic enol ethers yielded acyclic diols as the only product. A plausible mechanism has been proposed for this unusual reaction in **Scheme III.2.4.**

Table III.2.2

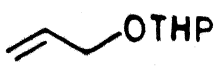
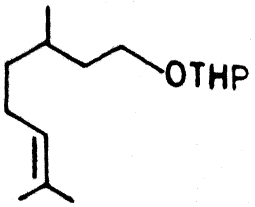
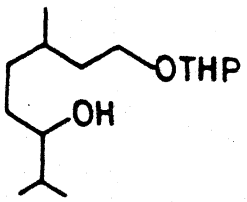
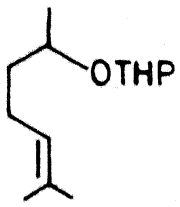
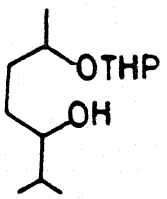
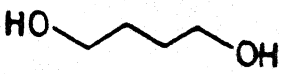
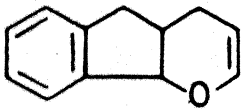
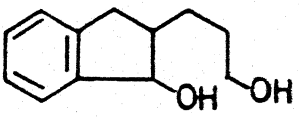
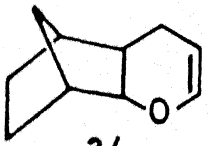
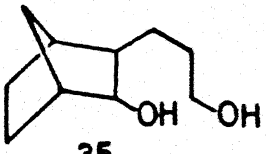
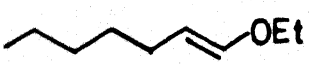
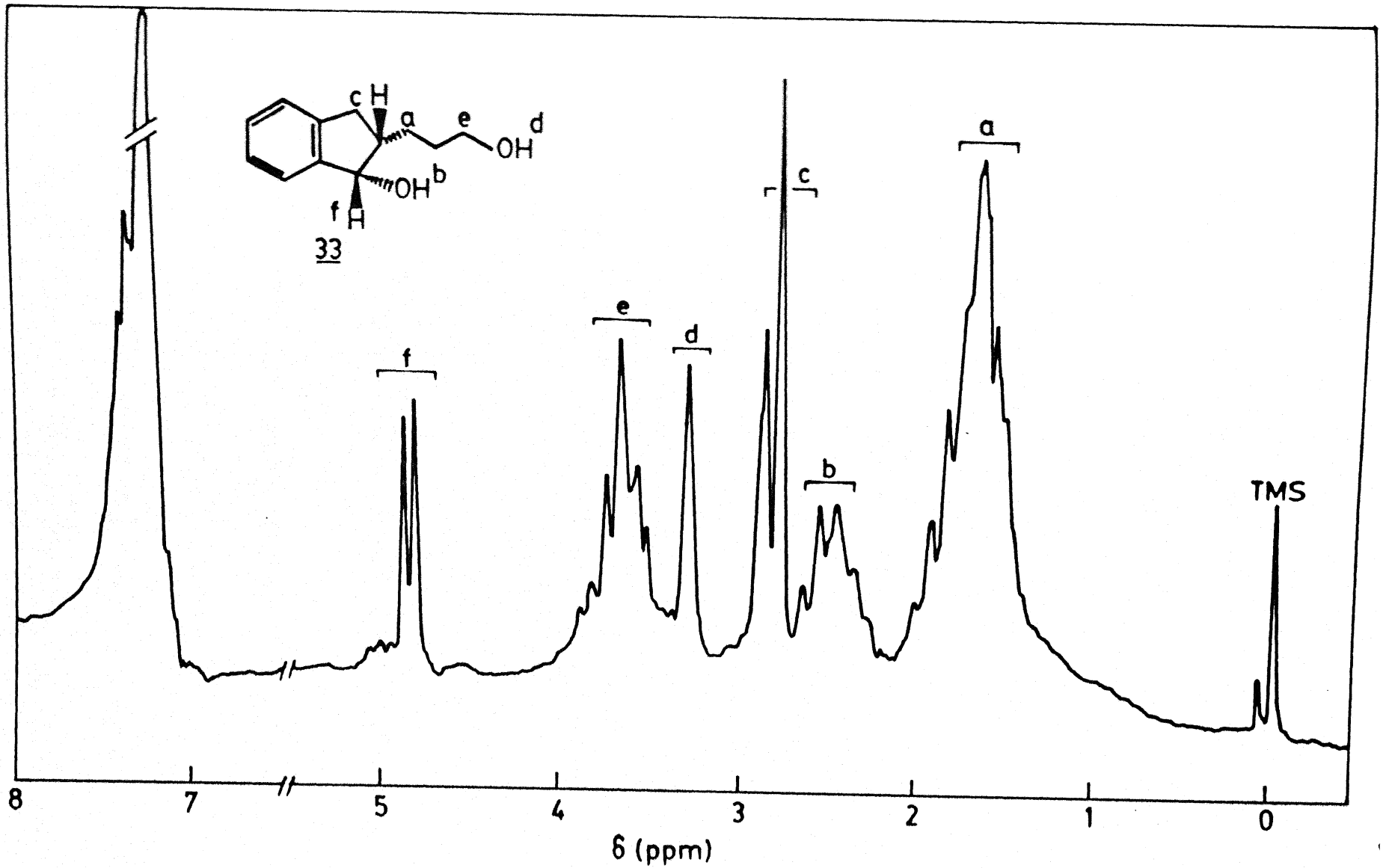
Entry	Substrate	Product	Time	Yield %
1	 22	 23	6	68
2	 24	 25	5	64
3	 26	 27	7	59

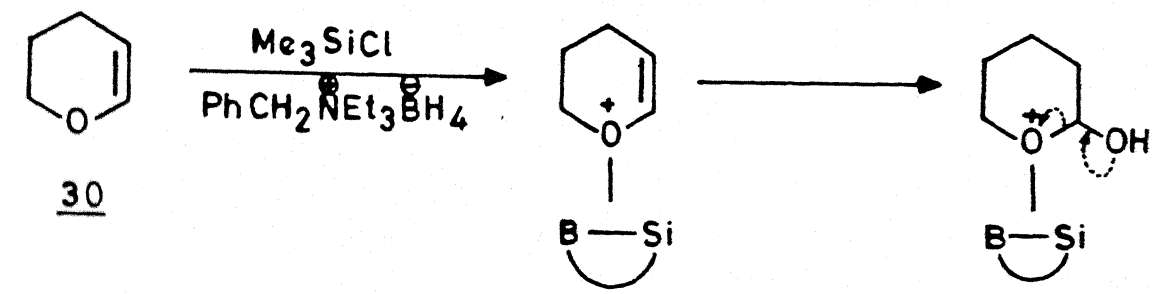
Table III.2.3

Entry	Substrate	Product	Time	Yield %
1	 28	 29	8	73
2	 30	 31	8	74
3	 32	 33	10	83
4	 34	 35	8	68
5	 36	 37	6	80

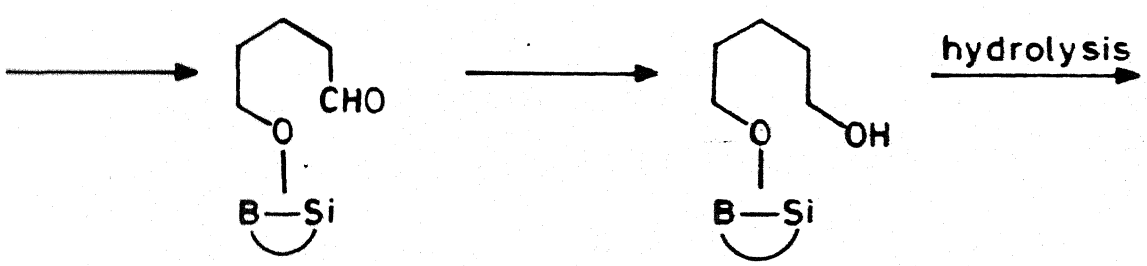


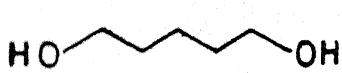
^{1}H NMR Spectrum (80 MHz) of 33

Scheme III.2.4



30





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B—Si = boron-silicon reactive complex

In summary this present synthetic methodology using benzyltriethylammonium borohydride chlorotrimethylsilane will be complimentary to the normal hydroboration-oxidation of olefins. Since the reactivity of this reagent system is different from that of BH_3THF, the scope and limitations of this reagent system and its reactivity with other organic substrates need to be explored in future.

III.3 EXPERIMENTAL

General Procedure

As described in Chapter IA.

Materials

Chlorotrimethylsilane (Fluka) was distilled over calcium hydride. Benzyltriethylammonium chloride (Aldrich) was used as such. Dichloromethane was distilled over P_2O_5.

Chromatography

As described in Chapter IA.

Physical Data

As described in Chapter IA.

Preparation of Benzyltriethylammonium borohydride[29]

To a stirred solution of benzyltriethylammonium chloride (22.7 g, 0.1 mol) in 5 M aqueous sodium hydroxide solution (20 mL) at room temperature was added a solution of sodium borohydride (4.536 g, 0.12 mol) in 5 M aqueous sodium hydroxide (10 mL). The resulting mixture was stirred at room temperature

for 0.5 h and then extracted with dichloromethane (3x100 mL). The combined organic layers were dried over anhydrous potassium carbonate and the solvent was evaporated to yield solid benzyltriethylammonium borohydride. The crude solid was washed with dry ether and dried under vacuum to afford crystalline white solid (20.08 g, 97%), m.p. 145-147 ^{o}C.

IR (KBr) : 2990, 2290, 2210, 1450 cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ -0.22, 0.56, 0.78 and 1.59 (4s, 4 H), 1.34-1.5 (t, 9 H), 3.22-3.53 (q, 6 H), 4.59 (s, 2 H), 7.5 (d, 5 H).

General Procedure for the Conversion of Alkenes to Alcohols

Reaction of Camphene 1 With $PhCH_2N^{+}Et_3B^{-}H_4/Me_3SiCl$

To a stirred solution of camphene **1** (0.544 g, 4 mmol) and benzyltriethylammonium borohydride (0.828 g, 4 mmol) in dry dichloromethane (6 mL) at 0 ^{o}C was added chlorotrimethylsilane (0.432 g, 4 mmol) in dichloromethane (2 mL) and the reaction mixture was stirred for 3 h. A solution of 10% K_2CO_3 (3 mL) was added and stirred for an additional 0.25 h. Dichloromethane was removed under vacuum and the residue was extracted with ether (3x10 mL). The combined organic layers were washed with brine solution and dried over anhydrous $MgSO_4$. The solvent was evaporated and the crude product was purified by flash chromatography on silica gel (ether-petroleum ether, 1:20) to yield the hydrocarbon **2c** (0.094 g, 17%).

^{1}H NMR ($CDCl_3$) : δ 0.88 (s, 3 H), 0.90 (d, 3 H), 0.93 (s, 2H), 1.0 (s, 3 H), 1.20-1.52 (m, 4 H), 1.63-1.83 (m, 3 H).

Further elution (1:5, ether-petroleum ether) afforded the alcohol **2**[39] (0.493 g, 80%) as an oil.

IR (neat) : 3460 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 0.88 (s, 3 H), 0.93 (s, 2 H), 1.0 (s, 3 H), 1.19-1.5 (m, 4 H), 1.63-1.82 (m, 3 H), 2.25 (br,s, 1 H), 3.63-3.72 (d, 2 H).

Reaction of trans-Stilbene 3

A mixture of trans-stilbene **3** (0.72 g, 4 mmol) and benzyltriethylammonium borohydride (0.828 g, 4 mmol) in dry dichloromethane (6 mL) at 0 °C was treated with chlorotrimethylsilane (0.432 g, 4 mmol) in dichloromethane (2 mL) at 0 °C for 8 h. After the usual work-up, the crude product was purified by flash chromatography on silica gel (ether-petroleum ether, 1:10) to yield 1,2-diphenylethane **4c** (0.058 g, 8%) as a solid, m.p. 50-52 °C.

IR (KBr) : 3060, 3020, 1600 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 2.92 (s, 4 H), 7.24 (d, 10 H).

Further elution (1:5, ether-petroleum ether) gave 1,2-diphenylethanol **4** (0.618 g, 78%).

IR (KBr) : 3530, 3060, 3020, 1600 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 2.41 (s, 1 H), 3.0-3.1 (d, 2 H), 4.87 (t, 1 H), 7.2-7.37 (m, 10 H).

Compounds **4** and **4c** were found to be identical in all respects with the authentic samples.

Reaction of Cyclooctene 5

Cyclooctene **5** (0.44 g, 4 mmol), benzyltriethylammonium borohydride (0.828 g, 4 mmol) and chlorotrimethylsilane (0.432 g, 4 mmol) in dichloromethane at 0 °C, were allowed to react for 0.5 h as described earlier to give the hydrocarbon **6c** (0.081 g, 18%) and alcohol **6** (0.379 g, 74%), after chromatographic purification (1:10, ether-petroleum ether).

compound 6c : b.p. 70 °C/20 mm.

IR (neat) : 2970 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.54 (s, 16 H).

compound 6 : b.p. 106-108 °C/22 mm.

IR (neat) : 3560, 2980 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.55 (br,s, 14 H), 2.61 (br,s, 1 H), 3.65 (t, 1 H).

Compounds **6** and **6c** were found to be identical in all respects with the authentic samples.

Reaction of Olefin 7

Under similar reaction conditions, olefin **7** (0.504 g, 4 mmol), on treatment with benzyltriethylammonium borohydride (0.828 g. 4 mmol) and chlorotrimethylsilane (0.432 g, 4 mmol), yielded the hydrocarbon **8c** (0.092 g, 18%) and alcohol **8** (0.415 g, 72%), after chromatographic purification (1:10, ether-petroleum ether).

compound 8c : b.p. 62 °C/20 mm.

IR (neat) : 2990, 2970 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 0.87 (t, 6 H), 1.28 (br,s, 14 H).

compound 8 : b.p. 97 °C/10 mm.

IR (neat) : 3490 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 0.87 (t, 1 H), 1.18-1.43 (br,s, 14 H), 2.41 (br,s, 1 H), 3.86 (t, 2 H).

Compounds **8** and **8c** were found to be identical in all respects with the authentic samples.

Reaction of 1-Phenyl cyclohexene 9

A mixture of 1-phenyl cyclohexene **9** (0.632 g, 4 mmol), benzyltriethylammonium borohydride (0.828 g, 4 mmol) in dichloromethane at 0 °C was treated with chlorotrimethylsilane (0.432 g, 4 mmol). The resulting mixture was stirred at 0 °C for 4 h. After the usual work-up, the crude product was purified by flash chromatography on silica gel (1:10, ether-petroleum ether) to give phenylcyclohexane **10c** (0.058 g, 9%) and then cis-2-phenylcyclo hexanol **10b**[40] (0.148 g, 21%).

compound 10c : b.p. 110 °C/7 mm.

IR (neat) : 3020, 1600 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.0-1.6 (m, 5 H), 1.6-2.1 (m, 5 H), 2.5 (m, 1 H), 7.28 (s, 5 H).

compound 10b[40] : m.p. 40-41 °C (lit.[40] m.p. 40-41 °C).

IR ($CHCl_3$) : 3480, 3080, 3060, 3020, 1610 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.53-1.86 (m, 8 H), 1.97 (br,s, 1 H), 2.68, 2.84 (2 t, 1 H), 4.03 (br,s, 1H), 7.36 (s, 5 H).

On further elution, afforded trans-2-phenylcyclohexanol **10a**[41]

(0.444 g, 63%), m.p. 53-55 °C.

IR (KBr) : 3430, 3070, 3050, 3020, 1600 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.31-1.84 (m, 8 H), 2.11 (br,s, 1 H), 2.43 (m, 1 H), 3.66 (sextet, 1 H), 7.38 (br,s, 5 H).

Reaction of (±)α-Pinene 11

When a mixture of α-pinene **11** (0.544 g, 4 mmol), benzyltriethylammonium borohydride (0.828 g, 4 mmol) in dichloromethane (6 mL) at 0 °C was treated with chlorotrimethylsilane (0.432 g, 4 mmol) for 3 h. Compound **12c**[42b] (0.061 g, 11%), compound **12b**[42b] (0.062 g, 10%) and compound **12a**[42] (0.444 g, 72%) were isolated after chromatographic purification (1:10, ether-petroleum ether).

compound 12a[42] : m.p. 35-36 °C.

IR (KBr) : 3350, 1388, 1370 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 0.92 (s, 3 H), 1.0 (d, 3 H), 1.21 (s, 3 H), 3.56 (m, 1 H).

compound 12b[42b]:

IR (neat) : 3440, 1390. 1370 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 0.77 (s, 3 H), 0.93 (d, 3 H), 1.21 (s, 3 H), 3.99 (m, 1 H).

compound 12c[42b]:

IR (neat) : 1388, 1370 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 0.90 (s, 3 H), 0.94 (d, 3 H), 1.21 (s, 3 H).

Reaction of (+)α-Pinene 11

A mixture of (+)α-pinene **11** (0.544 g, 4 mmol) and benzyltriethylammonium borohydride (0.828 g, 4 mmol) in dichloromethane was treated as above with chlorotrimethylsilane (0.432 g, 4 mmol) for 3 h, to yield, after chromatographic purification, (-) isopinocampheol **12a**[42b] (0.456 g, 74%), m.p. 54-56 °C (lit.[42b] 55-57 °C; $[\alpha]_D^{20}$ - 31.9 ° (C 10, C_6H_6) (lit.[42b] $[\alpha]_D^{20}$ - 32.8 ° (C 10, C_6H_6), (+) neo-isopinocampheol **12b**[42b] (0.062 g, 10%), m.p. 45-48 °C (lit.[42b] 45-47 °C), $[\alpha]_D^{20}$ + 35.3 ° (C 3, C_6H_6) (lit.[42b] $[\alpha]_D^{20}$ + 36 ° (C 3, C_6H_6) and (+) cis-pinane **12c**[42b] (0.044 g, 8%) $[\alpha]_D^{20}$ - 20.1 ° (C 4, $CHCl_3$) (lit.[42b] $[\alpha]_D^{20}$ - 20.9 ° (C 4, $CHCl_3$).

Spectral data of compounds **12a**, **12b** and **12c** were found to be identical with the spectra of those prepared earlier.

Preparation of Compound 13[37]

To a stirred solution of 1,4-butanodimagnesium bromide, derived from magnesium powder (0.583 g, 24 mg atom) and 1,4-dibromobutane (2.16 g, 10 mmol) in dry tetrahydrofuran (20 mL) at -12 °C was added a solution of cis-endo-5-norborn-5-en-2,3-dicarboxylic anhydride[43] (1.64 g, 10 mmol) in dry tetrahydrofuran (10 mL). The resulting reaction mixture was stirred at this temperature for 3 h and then stirred at room temperature for an additional 8 h. After hydrolysis with 10% hydrochloric acid (10 mL), the organic layer was separated and the aqueous layer was extracted with ether (2x50 mL). The combined organic layers were washed with sodium bicarbonate solution, brine and dried over anhydrous $MgSO_4$. The solvent was evaporated to yield the

crude product **13**, which was recrystallized from ether-petroleum ether to give the spirolactone **13**[37] as white flakes (1.326 g, 65%); m.p. 70-71 °C (lit.[37] m.p. 74-75 °C).

IR (KBr) : 3060, 1760 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.3-1.9 (m, 10 H), 2.89 (dd, 1 H), 3.11 (t, 1 H), 3.37 (m, 1 H), 3.39 (dd, 1 H), 6.23 (br,s, 2 H).

MS (m/e) : 205 (M^++1), 139, 138, 66.

Reaction of Compound 13

A mixture of compound **13** (0.816 g, 4 mmol) and benzyltriethylammonium borohydride (0.828 g, 4 mmol) was allowed to react with chlorotrimethylsilane (0.432 g, 4 mmol) for 2 h, to give the regio-isomeric alcohols **14**[44] (0.604 g, 68%) and saturated compound **14c**[44] (0.074 g, 9%) after chromatographic purification.

compound 14

IR ($CHCl_3$) : 3400, 1750 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.0-2.28 (m, 12 H), 2.28-2.81 (m, 3 H), 2.81-3.41 (m, 2 H), 3.81-4.26 (m, 1 H).

compound 14c

IR ($CHCl_3$) : 1760 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.03-2.32 (m, 14 H), 2.28-2.81 (m, 3 H), 2.82-3.02 (m, 1 H).

Reaction of Diphenylacetylene 15

Diphenylacetylene **15** (0.712 g, 4 mmol) was treated under similar conditions with benzyltriethylammonium borohydride

(0.828 g, 4 mmol) and chlorotrimethylsilane (0.432 g, 4 mmol) for 10 h, to give 1,2-diphenylethane **4c** (0.095 g, 13%) and 1,2- diphenylethanol **4** (0.554 g, 70%) after flash chromatography. Compounds **4** and **4c** were found to be identical in all respects with the authentic samples.

Reaction of Diphenylacetylene 15 Under Controlled Conditions

A mixture of diphenylacetylene **15** (0.356 g, 2 mmol) and benzyltriethylammonium borohydride (0.414 g, 2 mmol) in dichloromethane at 0 °C, was treated with chlorotrimethylsilane (0.216 g, 2 mmol) for 3 h. After the usual work-up, nmr analysis of the product revealed the presence of 1:2 mixture of cis and trans-stilbene (12%).

Reaction of trans-2-Phenylcyclohexanol 10a

When trans-2-phenylcyclohexanol **10a** (0.176 g, 1 mmol) was treated with benzyltriethylammonium borohydride (0.207 g, 1 mmol) and chlorotrimethylsilane (0.108 g, 1 mmol) in dichloromethane for 2 h. Phenylcyclohexane **10c** (0.024 g, 15%) and unreacted starting material **10a** (0.141 g, 80%) were obtained after flash chromatography (1:10, ether-petroleum ether) **10c** was found to be identical with an authentic sample of phenylcyclohexane.

Reaction of 5 with MeI/$PhCH_2N^+Et_3B^-H_4$

A mixture of cyclooctene **5** (0.22 g, 2 mmol) and benzyltriethylammonium borohydride (0.414 g, 2 mmol) in dichloromethane (6 mL) at 0 °C was treated with a solution of methyl

iodide (0.284 g, 2 mmol) in dichloromethane (2 mL) for 3 h. Dichloromethane was removed under vacuum, and the residue was extracted with dry ether. The ether layer was concentrated under reduced pressure to give organoborane **16** (0.218 g, 95%).

IR (neat) : 2990, 2260, 2190 cm^{-1}

^1H NMR ($CDCl_3$) : δ 1.68 (br,s, 14 H), 4.2 (br,s, 1 H).

This compound **16** does not form the alcohol **6** on treatment with water, but gives alcohol **6** after the formal oxidative work-up.

Reaction of 5 with $Bu_3SnCl/PhCH_2N^+Et_3B^-H_4$

A mixture of **5** (0.22 g, 2 mmol) and benzyltriethylammonium borohydride (0.414 g, 2 mmol) in dichloromethane was treated with Bu_3SnCl (0.651 g, 2 mmol) at 0 °C for 6 h. Dichloromethane was removed under vacuum and the residue was extracted with dry ether. The solvent and low boiling compounds were removed under vacuum to yield the organoborane **16** (0.200 g, 87%) which was found to be identical with the sample prepared earlier.

Reaction of 5 with Free B_2H_6/Me_3SiCl

Pure diborane gas was generated by the addition of methyl iodide (0.568 g, 4 mmol) to a solution of benzyltriethylammonium borohydride (0.828 g, 4 mmol) in dichloromethane (3 mL) at 25 °C and it was passed through a solution of chlorotrimethylsilane (0.432 g, 4 mmol) in dichloromethane (5 mL) at 0 °C. To this mixture, olefin **5** (0.44 g, 4 mmol) was added at 0 °C and the resulting reaction mixture was stirred at the same temperature for 4 h. The solvent was removed under vacuum to yield the organoborane **16** (0.459 g, 100%).

Reaction of 5 with Free B_2H_6/$PhCH_2N^+Et_3Cl^-$/Me_3SiCl

Diborane gas, generated by the addition of methyl iodide (0.284 g, 2 mmol) to benzyltriethylammonium borohydride (0.414 g, 2 mmol), was passed through a solution of chlorotrimethylsilane (0.216 g, 2 mmol) and benzyltriethylammonium chloride (0.454 g, 2 mmol) in dichloromethane (3 mL) at 0 °C. To this mixture, **5** (0.22 g, 2 mmol) was added, the reaction mixture was stirred at 0 °C for 4 h and then dichloromethane was removed under vacuum. The residue was extracted with dry ether and solvent was removed under vacuum to yield pure organoborane **16** (0.225 g, 98%), which was found to be identical with the sample prepared earlier.

Reaction of 5 with Free B_2H_6/Et_3SiH

Diborane gas (2 mmol) was passed through a solution of Et_3SiH (0.232 g, 2 mmol) in dichloromethane (3 mL) at 0 °C. To this mixture olefin **5** (0.22 g, 2 mmol) was added at 0 °C and the resulting mixture was stirred for 4 h. Dichloromethane and Et_3SiH were removed under vacuum to yield pure organoborane **16** (0.230 g, 100%).

Reaction of 5 with $Ph_2MeSiCl$/$PhCH_2N^+Et_3B^-H_4$

A mixture of **5** (0.22 g, 2 mmol) and benzyltriethylammonium borohydride (0.414 g, 2 mmol) in dichloromethane (3 mL) at 0 °C was treated with $Ph_2MeSiCl$ (0.466 g, 2 mmol) in dichloromethane (2 mL) for 3 h. After the usual work-up, the crude product was purified by flash chromatography on silica gel (1:10, ether-petroleum ether) to yield Ph_2MeSiH (0.206 g, 52%)

and alcohol **6** (0.172 g, 67%). Compound **6** was found to be identical with the sample prepared earlier.

Ph_2MeSiH : B.p. 93-94 °C.

IR (neat) : 3020, 2990, 2970, 2085, 1400 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 0.64 (d, 3 H), 4.92 (q, 1 H), 7.28-7.44 (m, 6 H), 7.48-7.64 (m, 4 H).

Reaction of 5 with $NaBH_4/Me_3SiCl$

Olefin 5 (0.22 g, 2 mmol) and $NaBH_4$ (0.078 g, 2 mmol) in dry dimethoxyethane (DME) at 0°C were allowed to react with chlorotrimethylsilane (0.216 g, 2 mmol) for 2 h. The reaction mixture was quenched with 10% K_2CO_3 solution (2 mL) and extracted with ether. The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by flash chromatography on silica gel (1:20, ether-petroleum ether) to yield cyclooctanol **6** (0.161 g, 63%).

Reaction of 5 with $Me_3SiCl/PhCH_2N^+Et_3B^-H_4/N_2$

A mixture of 5 (0.22 g, 2 mmol) and benzyltriethylammonium borohydride (0.414 g, 2 mmol) in dry degased dichloromethane under nitrogen at 0 °C was treated with a solution of chlortrimethylsilane (0.216 g, 2 mmol) in degased dichloromethane under nitrogen for 1 h. After the usual work-up the crude product was purified by flash chromatography, to give cyclooctanol **6** (0.128 g, 50%), which was compared with the sample prepared earlier.

Reaction of Et_3N with $PhCH_2N^+Et_3B^-H_4/Me_3SiCl$

To a stirred solution of benzyltriethylammonium borohydride (0.414 g, 2 mmol) in dichloromethane (3 mL) at 0°C was added a solution of chlorotrimethylsilane (0.216 g, 2 mmol) in dichloromethane. The reaction mixture was stirred at 0 °C for 0.25 h and then it was treated with triethylamine (0.101 g, 1 mmol). After the usual work-up, the crude product was purified by flash chromatography on silica gel (eluent: ether-petroleum ether, 1:10) to give triethylamine complex (0.150 g) as a colorless liquid.

IR (thin film) : 2290, 2240 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 0.0-0.1 (2s).

^{11}B NMR ($CDCl_3$) : -35.1 (q).

General Procedure for the Preparation of Tetrahydropyranyl Ethers

Preparation of -OTHP Ether 22

To a stirred solution of allyl alcohol (0.29 g, 5 mmol) in dry dichloromethane (5 mL) at 0 °C was added freshly distilled dihydropyran (0.63 g, 7.5 mmol) followed by p-toluenesulfonic acid (0.01 g, 0.06 mmol) and stirred at 0 °C for 4 h. The reaction mixture was diluted with ether (30 mL), washed with aqueous bicarbonate solution, brine and dried ($MgSO_4$). The solvent was evaporated to obtain an oil which was purified by flash chromatography on silica gel (1:10, ether-petroleum ether) to get 22 as an oil (0.696 g, 98%).

^{1}H NMR ($CDCl_3$) : δ 1.59 (br,s, 6 H), 3.59-3.90 (m, 2 H), 4.21-4.84 (m, 3 H), 4.94-5.16 (m, 2 H), 5.66-6.18 (m, 1 H).

Preparation of -OTHP Ether 24

A mixture of citronellol (0.78 g, 5 mmol), dihydropyran (0.63 g, 7.5 mmol) and p-toluenesulfonic acid (0.01 g. 0.06 mmol) in dichloromethane was stirred at 0 °C for 3 h. After the usual work-up, the crude product was purified by flash chromatography to yield **24** (1.152 g, 96%) as an oil.

IR (neat) : 3080, 1630, 1230-1080 cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ 0.94 (d, 3 H), 1.25-1.53 (m, 11 H), 1.59 (s, 3 H), 1.66 (s, 3 H), 1.91-2.09 (m, 2 H), 3.28-3.59 (m, 2 H), 3.66-3.91 (m, 2 H), 4.5 (br,s, 1 H), 5.03 (t, 1 H).

Preparation of -OTHP Ether 26

6-Methyl-hept-5-en-2-ol (0.64 g, 5 mmol) was allowed to react with dihydropyran (0.63 g, 7.5 mmol) and p-toluene sulfonic acid (0.01 g, 0.06 mmol) in dichloromethane at 0 °C for 5 h. After the usual work-up, the crude product was purified by flash chromatography on silica gel, to afford **26** (0.869 g, 82%) as an oil.

IR (neat) : 3080, 1640, 1240-1070 cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ 1.06, 1.18 (2d, 3 H), 1.34-1.52 (m, 8 H), 1.56 (s, 3 H), 1.63 (s, 3 H), 1.78-2.03 (m, 2 H), 3.28-3.5 (m, 1 H), 3.56-3.81 (m, 2 H), 4.46-4.59 (m, 1 H), 5.0 (m, 1 H).

Reaction of 22 with $PhCH_2N^+Et_3B^-H_4/Me_3SiCl$

A mixture of compound **22** (0.284 g, 2 mmol) and benzyltriethylammonium borohydride (0.414 g, 2 mmol) in dichloromethane (4 mL) at 0 °C was treated with chlorotrimethylsilane (0.216g, 2 mmol) for 6 h. After the usual work-up, the crude product was purified by distillation to afford compound **23** (0.218 g, 68%), b.p. 62-63 °C/0.1 mm (lit.[45] b.p. 61 °C/0.09 mm).

IR (neat) : 3460, 1230-1060 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.41-1.91 (m, 9 H), 3.28-3.59 (m, 4 H), 3.63-3.84 (m, 2 H), 4.5 (br,s, 1 H).

Reaction of Compound 24

A mixture of compound **24** (0.480 g, 2 mmol), benzyltriethylammonium borohydride (0.414 g, 2 mmol) and chlorotrimethylsilane (0.216 g, 2 mmol) was stirred for 5 h at 0 °C). After the usual work-up the product was purified by flash chromatography to yield **25** (0.330 g, 64%).

IR (neat) : 3450, 1230-1070 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 0.81-0.88 (d, 9 H), 1.22 (br,s, 6 H), 1.38-1.69 (m, 9 H), 3.25-3.53 (m, 3 H), 3.59-3.8 (m, 2 H), 4.47 (br,s, 1 H).

Reaction of Compound 26

Chlorotrimethylsilane (0.216 g, 2 mmol) was allowed to react with a mixture of compound **26** (0.424 g, 2 mmol) and benzyltriethylammonium borohydride (0.414 g, 2 mmol) in dichloromethane at 0 °C for 7 h. The crude product obtained was purified

methane was treated with chlorotrimethylsilane (0.432 g, 4 mmol) as above for 8 h. After the usual work-up, the crude product was purified by distillation under vacuum to yield 1,5-pentanediol **31** (0.308 g, 74%), b.p. 119°C/10 mm which was found to be identical with an authentic sample 1,5-pentanediol.

Preparation of 5,6-Indenyldihydro-2H-pyran 32[46]

Indene (5 g, 43 mmol) and acrolein (7.24 g, 129.13 mmol) were sealed in a glass tube under N_2. This was heated in an oil bath at 140 °C for 10 h. The seal was carefully broken after the contents were cooled in an ice bath. The crude reaction product was purified over basic alumina to recover unreacted starting material indene (2.3 g) and the adduct **32**[46] (1.6 g, 40%) as a pale yellow oil.

IR (neat) : 3030, 1650, 1235, 1085, 1060 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.81-2.33 (m, 2 H), 2.86 (m, 2 H), 4.53-4.76 (dt, 2 H), 5.17 (d, 1 H), 6.52 (dt, 1 H), 7.29 (d, 4 H).

Reaction of 32

Compound **32** (0.344 g, 2 mmol) was allowed to react for 10 h with benzyltriethylammonium borohydride (0.414 g, 2 mmol) and chlorotrimethylsilane (0.216 g, 2 mmol) in dichloromethane, as described earlier. After the usual work-up, the crude product was purified by flash chromatography on silica gel (1:4, ethyl acetate-petroleum ether) to afford the diol **33** (0.319 g, 83%).

IR (neat) : 3560, 3020, 1610 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.41-1.88 (m, 4 H), 2.25-2.66 (m, 2 H), 2.81

(d, 2 H), 3.28 (s, 1 H), 3.5-3.81 (m, 2 H), 4.84 (d, 1 H), 7.25 (br,s, 4 H).

MS (m/e) : 174 (M^+-18), 159, 130, 115, 91, 77.

Preparation of 5,6-Norbornyl-3,4-dihydro-2H-pyran, 34[17]

A solution of freshly distilled acrolein (4.485 g, 0.08 mol), norbornylene (10 g, 0.106 mol) and BHT (2,6-di-tert-butyl p-cresol; 0.16 g) were introduced into a glass tube and sealed after cooling the contents in an ethanol-liquid nitrogen bath. The reaction mixture was then heated at 190 °C for 25 h. After expiry of the same, the seal was carefully broken (after cooling the contents in an ethanol-liquid nitrogen bath). The crude product on chromatographic purification over basic alumina (2% ether in petroleum ether 40-60 °C) gave the pure enol ether **34**[17] (6.515 g, 41%).

IR (neat) : 3050, 1640 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 2.09-2.41 (br,s, 2 H), 3.75 (d, 1 H), 4.92-5.16 (m, 1 H), 6.47 (dd, 1 H).

Reaction of Enol Ether 34

A mixture of enol ether **34** (0.3 g, 2 mmol) and benzyltriethylammonium borohydride (0.414 g, 2 mmol) in dichloromethane was treated with chlorotrimethylsilane (0.216 g, 2 mmol) for 8 h. The crude product was purified by flash chromatography on silica gel (1:4, ethyl acetate-petroleum ether) to yield the diol **35** (0.231 g, 68%).

IR ($CHCl_3$) : 3420 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 3.42 (t, 2 H), 3.68 (d, 1 H).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.59; H, 10.59.

Found : C, 70.63; H, 10.60.

Preparation of Heptaldehyde Diethyl Acetal[48]

Hexylmagnesium bromide was prepared from freshly distilled 1-bromohexane (4.127 g, 25 mmol) and magnesium powder (0.729 g, 30 mg atom) in dry ether (30 mL). It was cooled with ice water and triethylorthoformate (3.565 g, 24.05 mmol) in dry ether (20 mL) was added to it slowly with stirring.. After the addition was over, it was refluxed for 6 h and worked up by adding slowly to an excess of saturated aqueous ammonium chloride solution and then extracted with ether. Ether extracts were dried over anhydrous $MgSO_4$, the solvent was evaporated and the crude product was distilled under reduced pressure to give heptaldehyde diethyl acetal[48] (3.961 g, 88%) as an oil; b.p. 79-81 ^{o}C/8 mm (lit. b.p. 204-205 ^{o}C/774 mm).

IR (neat) : 2940, 1455, 1370, 1125, 1055 cm^{-1}.

^1H NMR (CCl_4) : δ 0.9 (t, 3 H), 1.1-1.47 (m, 16 H), 3.47 (m, 4 H), 4.4 (t, 1 H).

Preparation of 1-Ethoxy heptene 36[49]

Magnesium bromide was prepared from 1,2-dibromoethane (5.25 g, 27.93 mmol) and magnesium powder (0.747 g, 30.72 atom) in dry ether (25 mL) under N_2. Dry benzene (16 mL) was added and refluxed for 0.5 h to remove the ether. It was cooled to room temperature and triethylamine (2.83 g, 27.93 mmol) was added with stirring. After 0.5 h, heptaldehyde diethyl acetal (3.5 g, 18.62 mmol) in dry benzene (5 mL) was added dropwise and

refluxed for 24 h and worked up by carefully adding a saturated ammonium chloride solution and then extracted with ether. Ether extracts were dried over anhydrous K_2CO_3 and the solvent was evaporated to yield a residue which was distilled under reduced pressure to get 1-ethoxy heptene **36**[49] (1.59 g, 60%) as a colorless oil; b.p. 64-66 ^oC/20 mm (lit. b.p. 61 ^oC/16 mm).

IR (neat) : 3020, 1650, 1450 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 0.89 (t, 3 H), 1.06-1.34 (m, 9 H), 2.06 (m, 2 H), 3.8 (q, 2 H), 4.4 (q, 1 H), 6.0 (d, 1 H).

Reaction of 1-Ethoxy heptene 36

Enol ether **36** (0.284 g, 2 mmol), benzyltriethylammonium borohydride (0.414 g, 2 mmol) and chlorotrimethylsilane (0.216 g, 2 mmol) in dichloromethane was stirred for 6 h to yield 1-heptanol **37** (0.186 g, 80%). It was distilled at 72 ^oC/11 mm and was found to be identical with an authentic sample.

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